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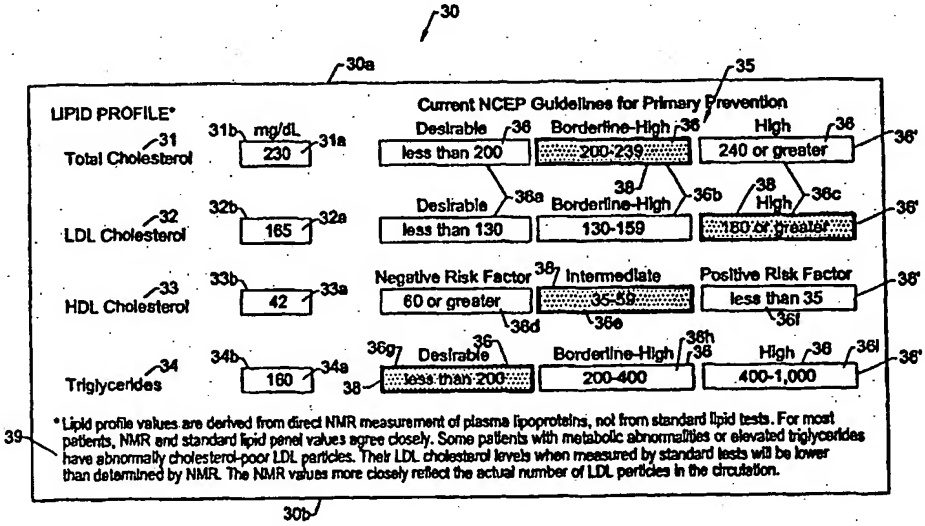

(57) Abstract

A method for analyzing a patient's risk of coronary heart disease by determining the presence of NMR-derived or based lipoprotein constituent value abnormalities includes determining the presence of atherogenic dyslipidemia based on the existence of a clustering of lipoprotein constituent abnormalities as defined by predetermined test criteria. Computer program products and automatically produced reports for presenting NMR-derived lipoprotein risk assessment based on patient-specific lipoprotein subclass results present the measurement results adjacent to a segmented reference risk analysis portion. The actual measured results are visually aligned and enhanced within the risk analysis portion to provide easy reference and understanding of the results relative to a risk of developing coronary heart disease.

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METHODS, SYSTEMS, AND COMPUTER PROGRAM PRODUCTS FOR ANALYZING AND PRESENTING RISK ASSESSMENT RESULTS BASED ON NMR LIPOPROTEIN ANALYSIS OF BLOOD

Related Applications

This application is a continuation in part of U.S. Application Serial No. 09/258,740 filed 26 February 1999.

Field of the Invention

The present invention relates generally to analysing and reporting patient specific medical information.

Background of the Invention

Recently, a significant advance in measurement techniques used to analyze blood plasma lipoprotein samples was achieved. Lipoproteins are the spherical particles that transport cholesterol, triglycerides, and other lipids in the bloodstream. The advanced measurement technique employs NMR spectroscopy to provide additional (higher-order) patient-specific information over the types of information typically provided under routine conventional analysis methods. *See* U.S. Patent No. 4,933,844 to Otvos, entitled "*Measurement of Blood Lipoprotein Constituents by Analysis of Data Acquired From an NMR Spectrometer*" and U.S. Patent No. 5,343,389 to Otvos, entitled "*Method and Apparatus for Measuring Classes and Subclasses of Lipoproteins.*" The contents of these documents are hereby incorporated by reference as if recited in full herein. Unlike conventional "routine" laboratory lipoprotein blood tests, the lipoprotein analysis provided by the NMR spectral analysis now more easily provides lipoprotein subclass

information, which had, until this advance, been generally inaccessible to clinicians. This subclass information can provide information corresponding to the sizes of the lipoprotein particles that make up a person's lipoprotein constituents.

Lipoprotein subclass information is not included in conventional commercially prepared lipid panels. The conventional panels typically only provided information concerning total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol (generally a calculated value), and high-density lipoprotein (HDL) cholesterol. In contrast, the NMR analysis can provide information about (a) the concentrations of six subclasses of very low density lipoprotein (VLDL), four subclasses of LDL (including intermediate-density IDL), and five subclasses of HDL, (b) average LDL particle size (which can be used to categorize individuals into LDL subclass pattern-determined risk), and (c) LDL particle concentration.

The subclass information now available with the NMR spectral analysis can be a more reliable indicator of a patient's risk to develop coronary heart disease. Indeed, recent scientific research has shown that various subclasses of lipoproteins may provide more reliable markers of the metabolic conditions that predispose individuals to a greater or lesser risk of heart disease. However, the NMR spectral analysis can also provide higher-order information about the levels of variously atherogenic or antiatherogenic subclasses that make up each of the major lipoprotein classes.

This subclass information can provide a clear indication about a patient's propensity to develop coronary heart disease. Unfortunately, this additional information can confuse a reviewer as to the meaning of the data, and further, the additional information can be difficult to analyze in a readily discernable manner. For example, a typical NMR lipoprotein analysis can include at least fifteen more values of lipoprotein concentration and size than is provided by standard lipoprotein panels. There is, therefore, a need to analyze and present the lipoprotein-based information in a manner or format which is visually easy to read and understand and which provides a useful coronary heart disease risk assessment.

Objects and Summary of the Invention

It is therefore an object of the present invention to provide a method to analyze patient-specific NMR based lipoprotein measurements in a manner which yields a reliable indicator of an associated risk of developing coronary heart disease.

It is an additional object of the present invention to provide a lipoprotein profile analysis with subclass information with an easily read display format.

It is also an object of the present invention to provide a lipoprotein-based risk assessment which analyzes a patient's measured major lipoprotein constituent values and/or selected subclass information and presents them in a format in which a patient's specific values are presented in a reader-friendly format.

It is a further object of the present invention to provide a method of generating a customized report at a commercial volume and which can analyze and/or report a patient's risk factors for coronary heart disease based on NMR-based measurements of lipoprotein constituents.

It is still another object of the invention to alert the patient or physician of a reduced lipoprotein constituent value for a secondary prevention goal for patients with underlying metabolic disorders.

It is an additional object of the present invention to provide a system for measuring lipoprotein constituents and analyzing the constituent values in a manner which determines CHD risk.

These and other objects of the present invention are provided by a method for identifying a patient with an increased risk of coronary heart disease by analyzing the patient's NMR lipoprotein constituent measurements. This analysis includes determining a risk for a specific constituent identified as having an independently predictive factor (in isolation of the other constituent values) and for a combination of certain of the constituent measurement values. Preferably, the combination method identifies whether the patient's results provide a positive match with two key NMR measured lipoprotein factors. The first factor is the determination of the presence of atherogenic dyslipidemia (*i.e.*, a clustering of

predetermined level moderate, borderline, or positive NMR subclass or constituent based risk values) and the second factor is the detection of an elevated number of NMR measured LDL particles. Advantageously, this type of risk analysis is typically more accurate than the plasma apo B level techniques used in the past, and can provide a more reliable indictor as it more closely corresponds to a patient's true lipoprotein composition.

In particular, a first aspect of the present invention is directed to a method for assessing a patient's risk of coronary heart disease based on personalized NMR measured lipoprotein-based information. The method includes generating NMR-based lipoprotein measurement values for a patient's blood plasma or serum sample, the NMR-based lipoprotein measurement values comprising a plurality of lipoprotein constituent values including a constituent value for LDL particle concentration. The LDL particle concentration is compared with predetermined test criteria for determining whether the LDL particle concentration is elevated and a plurality of NMR-based lipoprotein constituent values are compared to predetermined test criteria to determine the presence of atherogenic dyslipidemia. A patient's risk of coronary heart disease is assessed based on one or more of the LDL particle elevated concentration level and the presence (or absence) of atherogenic dyslipidemia.

In a preferred embodiment, the NMR-based lipoprotein constituent values include the major lipoprotein constituents of total cholesterol, LDL concentration in cholesterol equivalents, HDL concentration in cholesterol equivalents, and triglycerides, and the measured lipoprotein constituent values also include the values associated with LDL size, LDL particles, large HDL cholesterol, and large VLDL triglyceride. It is also preferred that the NMR based lipoprotein constituent values used to determine the presence of atherogenic dyslipidemia is independent to the LDL particle concentration value (i.e., does not include the isolated LDL particle concentration value as part of the subtest criteria for determining atherogenic dyslipidemia). Preferably, the predetermined test criteria for determining the presence of an elevated number of LDL particles is set at a value which is in about the upper 50% of the population (at least moderately elevated).

Of course, the presence of atherogenic dyslipidemia when an elevated LDL particle concentration also exists is particularly indicative of the presence of a higher-risk metabolic condition.

Another aspect of the present invention is directed to a method of presenting NMR derived lipoprotein subclass information in a two-dimensional window. The method includes obtaining a plurality of lipoprotein constituent values associated with NMR based lipoprotein measurements including the values associated with LDL size, LDL particles, large HDL cholesterol, and large VLDL triglyceride and identifying a risk level associated with coronary heart disease for each of the obtained NMR based lipoprotein constituent values. The obtained lipoprotein constituent values are then analyzed to determine the associated risk level and the obtained lipoprotein constituent values are arranged in a display format which positions the lipoprotein constituent values adjacent to a corresponding risk analysis portion, wherein the risk analysis portion has a plurality of discrete segments characterizing the constituent value's determined risk level. The discrete risk segment corresponding to the actual constituent value within the respective risk analysis portion is visually enhanced such that the risk associated with the lipoprotein constituent value is readily apparent. Preferably, the obtaining step also obtains the NMR based lipoprotein constituent values for the major lipoprotein constituents of total cholesterol, LDL concentration in cholesterol equivalents, HDL concentration in cholesterol equivalents, and triglycerides. It is also preferred that the risk analysis for LDL concentration in cholesterol equivalents and the LDL particle concentration includes four discrete risk segments (corresponding to optimal, desirable, borderline-high, and high risk) and wherein each of the discrete risk segments corresponds to a predetermined level associated with its occurrence in the general population. Preferably, the remainder of the lipoprotein constituent values risk analysis segments are configured with three discrete segments, and the risk analysis discrete segments for the non-major lipoprotein constituent values are configured to mirror the risk level defined for the risk analysis discrete segments for the major lipoprotein

constituents. (Typically, the risk analysis segment defines the risk level such that it corresponds to the occurrence of the value as defined by a population percentile).

In a preferred embodiment, the optimal value is a reduced target value for secondary prevention.

Another aspect of the present invention is an automatically produced lipoprotein report including data corresponding to NMR-derived measurements. The report comprises a first lipid profile segment comprising a plurality of NMR derived major lipoprotein constituent values, wherein each major lipoprotein value has an associated risk analysis portion and a second subclass profile segment comprising a plurality of NMR derived subclass variables, each subclass variable having an associated risk analysis portion which is configured to visually enhance the risk of developing coronary heart disease for each of the plurality of subclass variable information. The lipoprotein report is generated at a commercial scale at automatically generated by a computer based on NMR derived patient-specific information. Further, at least the subclass profile segment includes a reduced target value associated with at least one subclass value associated with a goal of secondary prevention, thereby facilitating the awareness of the existence of an underlying metabolic disorder and providing a visual reminder to pursue a more aggressive reduction of at least one lipoprotein value compared to the general population.

In a preferred embodiment, the reduced target value is identified as an optimal risk category for both the LDL concentration in cholesterol equivalents and the LDL particle concentration in the risk analysis portions. It is also preferred that the report include a coronary heart disease risk assessment module. The risk assessment module provides additional information about coronary heart disease risks associated with an elevated number of LDL particles and the determination of the presence of atherogenic dyslipidemia associated with a clustering of selected abnormal subclass values.

Still another aspect of the invention is an automatically produced lipoprotein report which is generated at a commercial laboratory based on data corresponding to NMR-derived measurements. The automated report comprises a

subclass profile segment comprising a plurality of patient-specific NMR derived lipoprotein constituent values, each constituent value having an adjacently positioned associated risk analysis portion which visually identifies the value with one of at least three discrete risk categories corresponding to a coronary heart disease risk level associated with the NMR-derived measurement value. Preferably, the automatically produced lipoprotein report includes LDL particle concentration as one of the NMR derived lipoprotein constituent values and the corresponding risk analysis portion includes four risk categories: one associated with a desirable concentration level; one associated with a borderline-high level; one associated with an increased or higher risk level; and one associated with an optimal level corresponding to a goal for secondary prevention.

An additional aspect of the present invention is a computer program product for personalized lipoprotein-based risk assessment. The computer program product comprises a computer readable storage medium having computer readable program code means embodied in the medium. The computer-readable program code means comprising a computer readable program code means for generating NMR-based lipoprotein measurement values for a patient's blood sample, the lipoprotein measurement values including at least one subclass variable value. The computer program product also includes a computer readable program code means for comparing the at least one patient lipoprotein subclass variable value with predetermined test criteria for determining whether the at least one subclass variable value is associated with a higher or lower risk of developing coronary heart disease and computer readable program code means for identifying, for the at least one measured subclass variable value, the corresponding risk level associated with coronary heart disease. The computer program product also includes a computer readable program code means for providing a risk analysis portion adjacent to the measured lipoprotein values, the risk analysis portion displaying information corresponding to higher and lower coronary heart disease risk. The measured value is visually enhanced in the risk analysis portion to visibly indicate the level of risk associated therewith to thereby provide a contemporaneous reference guideline for interpretation of the measured value. The computer

program product additionally includes a computer readable program code means for comparing a plurality of the NMR-based lipoprotein measurement values to predetermined test criteria to determine the presence of atherogenic dyslipidemia.

In a preferred embodiment, the NMR-based lipoprotein values include the major lipoprotein constituents of total cholesterol, LDL concentration in cholesterol equivalents, HDL concentration in cholesterol equivalents, and triglycerides, and the subclass values associated with LDL size, LDL particles, large HDL cholesterol, and large VLDL triglyceride, and the computer program product further comprises computer readable program code means for presenting the lipoprotein measurement values such that each of the lipoprotein measurement values is substantially aligned. It is also preferred that the risk analysis portion for each of LDL concentration in cholesterol equivalents and LDL particles is divided into four risk categories, and that the remainder of the risk analysis portions is divided into three discrete segment risk categories.

Preferably, for the reports, methods, and computer program products directed to lipoprotein information, the measured lipoprotein values include (a) the major lipoprotein constituents of total cholesterol, LDL concentration in cholesterol equivalents, HDL concentration in cholesterol equivalents, and triglycerides and (b) the LDL size and the concentration level of LDL particles, large HDL cholesterol, and large VLDL triglyceride.

The present invention is advantageous because it provides NMR-derived lipoprotein results with associated risk information in a format that is easy to understand and aesthetically pleasing. Further, the patient's specific subclass profile is presented in the risk assessment report in a graphically enhanced or visually emphasized format so the clinician or layman can easily understand the risk category associated with one or more of a patient's subclass values. Further, the customized report is provided in a computer program product allowing mass or commercial level automated production of a summary report which includes a risk analysis portion which can be customized to report the patient's results in a visually enhanced format. Advantageously, the report or risk assessment method flags or alerts the treating physician or patient as to the reduced target goal for LDL

concentration and LDL particle concentration for patients with underlying metabolic disorders such as established or previously diagnosed coronary heart disease, diabetes, or other vascular disorders. This secondary prevention goal is preferably visibly presented to alert and facilitate the ongoing counseling for such a patient to reinforce the importance of behavioral modifications or other therapy.

Brief Description of the Drawings

Figure 1 illustrates a lipoprotein summary report according to the present invention.

Figure 2 illustrates a risk assessment report according to one embodiment of the present invention which may be included in or provided separate from the lipoprotein summary report of **Figure 1**.

Figure 2A illustrates an alternative embodiment of the risk report shown in **Figure 2.**

Figure 3 illustrates a lipid profile segment of the lipoprotein summary report of **Figure 1.**

Figure 4 illustrates a subclass profile segment of the lipoprotein summary report of **Figure 1.**

Figure 5 illustrates a supplemental risk factor segment of the risk assessment report of **Figure 2.**

Figure 6 illustrates a subclass level risk assessment segment for the risk assessment report of **Figure 2.**

Figure 7 illustrates a primary prevention risk assessment segment of the risk assessment portion of **Figure 2.**

Figure 7A illustrates a prevention risk assessment segment having positive risk factors identified as negative numbers to be added to negative risk factors having positive numbers such as those shown in **Figure 7** to provide an overall adjusted risk assessment according to the present invention.

Figure 8 illustrates a secondary risk segment including information regarding high-risk medical conditions for the risk assessment report of **Figure 2A.**

Figure 9 is a graphic illustration of alternative embodiment of subclass information and associated positive or negative risk with coronary heart disease.

Figure 10 is a flow chart of a method which analyzes and presents NMR derived lipoprotein information according to the present invention.

Figure 11 illustrates an alternate embodiment of a coronary heart disease analysis or lipoprotein measurement report.

Figure 11A illustrates the report of **Figure 11** with a modified subclass profile providing values associated with defined risk factors.

Figure 12 illustrates a risk assessment module identifying the presence of atherogenic dyslipidemia according to a preferred embodiment of the present invention.

Figure 12A illustrates an alternate embodiment of a risk assessment module according to the present invention.

Figure 13 illustrates yet another embodiment of a report according to the present invention.

Detailed Description of the Invention

The present invention now will be described more fully hereinafter with reference to the accompanying drawings, in which preferred embodiments of the invention are shown. This invention may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art. Like numbers refer to like elements throughout.

Referring now to **Figure 1**, a preferred embodiment of a NMR lipoprotein profile summary report **10** is shown. Preferably, the lipoprotein profile summary report **10** is divided into at least three horizontally oriented segments **20, 30, 40**. The first segment **20** of the summary report **10** includes patient identification data **21** such as a name, identification number, and any relevant personal history such as age, smoking status, and other related medical history. As shown, the first segment **20** can also include physician data **22** and a comment section **23**. The second

segment **30** of the summary report **10** presents the lipid profile analysis and will be discussed further below. The third segment **40** of the summary report **10** presents the subclass profile analysis and will also be discussed further below.

As shown in **Figure 2**, the summary report **10** can also include a risk assessment report **10'** containing information targeted to a more detailed risk assessment. Of course, the summary report **10** and the risk assessment report **10'** as well as individual segments of each can be individually reported, presented or provided. In any event, as shown, the risk assessment report **10'** includes a fourth segment **50** which presents supplemental risk factors, and a fifth segment **60** containing individual lipoprotein subclass levels. The summary report **10** can also include an optional sixth segment **70** which can incorporate primary prevention risk assessment information which can predict long term (*i.e.*, 10 year) coronary heart disease (CHD) risk percentages.

As shown in **Figure 2A**, a risk assessment report **10''** can also include a seventh segment **80** directed to secondary prevention guidelines which can summarize high risk conditions and characterizations, such as atherosclerotic vascular disease and diabetes, and general lipid management goals. This secondary prevention information may help to assist medical personnel in alternative treatment and to alert as to potential high-risk behavior or conditions. As shown, the risk assessment report is rearranged to present the fourth segment **50**, the sixth segment **60**, and the seventh segment **80**. The information in this sample risk assessment report **10''** is from a different patient than the results shown in **Figure 1** and **2**.

In a preferred embodiment, the major lipoprotein constituent values and the selected subclass values are generated via the NMR spectral analysis discussed above. The data are typically obtained by processing a blood plasma or serum sample obtained from a subject. As such, as used herein the terms "blood" and "plasma and "serum" sample are interchangeable, as each is suitable for obtaining the desired NMR spectroscopy signal.

Turning now to **Figure 3**, a preferred embodiment of the lipid profile or second segment **30** of the summary report **10** is shown. The patient-specific lipid

value results of total cholesterol **31**, LDL cholesterol **32**, HDL cholesterol **33**, and triglycerides **34** are listed and arranged in aligned order from a top portion **30a** of the second segment to a bottom portion **30b** of the second segment. Preferably, alongside the listed order of the total cholesterol, LDL, HDL, and triglycerides, **31**, **32**, **33**, and **34**, respectively, the associated actual measured values **31a**, **32a**, **33a**, and **34a** are also serially aligned. Preferably, the values **31a**, **32a**, **33a**, **34a** are each displayed in a box **31b**, **32b**, **33b**, **34b**. Of course, the values **31a**, **32a**, **33a**, and **34a** may otherwise be presented, but are preferably presented in a visually enhanced format (such as via bold, italics, shaded, font (size, type), circled, underlined, colored or highlighted by other visual enhancement means) to provide ready visual recognition of the patient-specific results.

As is also shown in **Figure 3**, the second segment **30** also preferably includes risk assessment guidelines **35** which represent a relative reference, guideline, or "yardstick" of the patient's value as compared to targeted values. Preferably, the risk assessment guidelines **35** divide the respective measured patient value for each of the total cholesterol **31**, LDL **32**, HDL **33**, and triglycerides **34** into three different categories **36** of risk associated with a predetermine range of values (shown as measured in mg/dL). These predetermined range of values are based on predetermined test criteria.

As shown, the three categories for total cholesterol **31** and LDL **32** are labeled desirable **36a**, borderline-high **36b**, and high **36c**. As shown, for total cholesterol **31**, the desirable **36a** category is defined as a value less than 200. For LDL **32**, the desirable category **36a**, is defined as a value less than 130. The borderline-high category **36b** is defined as a range of values between 200-239 for total cholesterol **31** and between 130-159 for LDL **32**. The high category **36c** is defined as 240 or greater for total cholesterol **31** and 160 or greater for LDL **32**.

Referring again to **Figure 3**, the HDL categories **36** are labeled as negative risk factor **36d**, intermediate **36e**, and positive risk factor **36f**. The negative risk factor **36d** is defined as a value of 60 or greater, the intermediate risk category **36e** is defined as a value between and including 35-59, and the positive risk factor **36f** is defined as a value less than 35.

The triglycerides categories **36** are labeled as normal **36g**, borderline-high **36h**, and high **36i**. The normal category **36g** is defined as a triglyderides value **33** of less than 200, the borderline-high category **36h** is defined as a value between 200-400, and the high category **36i** is defined as a value greater than 400 (but typically below 1000).

Preferably, the predetermined test criteria or targeted or ranges of values associated with each category of risk **36a-36i** are defined to correspond to current National Cholesterol Education Program (NCEP) guidelines for primary prevention of coronary heart disease. *See* National Cholesterol Education Program, *Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II)*, Circulation 1994; 89:1329-1445. Of course, other suitable values or definitions can also be used, such as population based norms or other targeted based norms.

Preferably, as shown in **Figures 1** and **3**, the risk category **36** which corresponds to the patient value is visibly enhanced so that a reader can readily discern the category associated with the patient specific result (*i.e.*, a visually enhanced risk category **38**). For example, a person reviewing the patient-specific results shown in **Figure 3** can readily discern that the patient results indicate that the patient is "high risk" in one category (LDL cholesterol **32**), intermediate/ borderline in two categories (cholesterol **31** and HDL cholesterol **33**), and desirable in the other category (triglycerides **34**). Further, a reviewer could readily discern how close the measured value is to the next adjacent risk category for each value **31, 32, 33, 34**, which can also facilitate a more complete understanding of the results.

Preferably, as shown, the risk assessment **35** is formatted so that the three risk categories **36** for each measured value are similarly sized and configured and are arranged serially over or under the adjacent measured value. In this way, each of the categories **36** for each measured value is positionally vertically aligned. The "low" or "negative/good" risk values **36a, 36d, 36g** are positioned on one edge of a risk bar **36'** and the "high" or "bad/positive" risk values **36c, 36f, 36i** are positioned at the opposing edge of the risk bar **36'**. This presentation yields an

aesthetic, easily readable format and informational horizontal continuum of risk characterization associated with the patient's results. As is also shown, the summary report **10** (or one or more of the segments **20, 30, 40**) can include a descriptive comment portion **39** which discusses slight differences which may be observed from NMR spectral measurements compared to conventional or standard tests.

Turning now to **Figure 4**, a preferred embodiment of the third segment **40** of the summary report **10** presenting the subclass profile is shown. The third segment **40** preferably includes four measured subclass variables, the subclass variables being labeled as LDL size **41**, LDL particles **42**, large HDL cholesterol **43**, and large VLDL triglyceride **44**. The LDL size value **41a** is shown as measured in nanometers (nm). The LDL particles value **42a** is shown as measured in nano-moles per liter (nmol/L) while the large HDL cholesterol value **43a** and the large VLDL triglyceride value **44a** are measured in milligrams per deciliter (mg/dL).

As for the lipid profile results discussed for the second segment **30** above, each of the measured values **41a, 42a, 43a, 44a** are preferably presented in a visually enhanced manner **41b, 42b, 43b, 44b** (the results are shown as visually enhanced or offset by a frame or box).

In a preferred embodiment, the third segment **40** also includes a risk assessment portion **46** where the measured results **41a, 42a, 43a,** and **44a** are visually enhanced and related or compared to predetermined criteria or values. For example, the LDL size result **41a** is associated with three risk categories **46a, 46b, 46c**. The risk categories **46a, 46b, 46c** are defined by a pattern (A, AB, or B, respectively) associated with the particle size. The first category **46a** is Pattern A, which is defined as a lower risk pattern associated with large particle sizes of 20.6-22.0 nm. The second category **46b** is Pattern AB which is defined as an intermediate risk and corresponds to a particle size of 20.4-20.5 nm. The third risk category **46c** is Pattern B and is defined as a higher-risk category and corresponds to smaller particle sizes of between 19.0-20.3 nm.

As shown, the remaining subclass measured values **42a, 43a, 44a,** are displayed on a horizontally oriented line graph **46'**. Preferably, each line graph **46'**

plots the patient's results to illustrate whether the result indicates a higher or lower risk of CHD. In the embodiment shown, the graph is used to compare the patient measured result against a percentage of the general population having higher or lower levels of the measured value. Preferably, as shown, the line graphs **46'** are plotted such that the results show a greater risk aligned at the right edge of the graph **46'**. Stated differently, whether a higher or lower value indicates a higher risk of CHD, each of the line graphs **46'** are defined to present the measured value such that the higher risk of CHD is at the same edge of the line graph and the higher and lower risks are thus visually aligned.

For example, the LDL particles **42a** and the large VLDL triglyceride values **44a** are graphed corresponding to percentage of the population having lower values **42c**, **44c** while the large HDL value **43a** is graphed corresponding to the percentage of population having a higher value **43c**. Nonetheless, as shown, the line graphs **46'** are oriented and plotted such that the higher risk of CHD is aligned along the right end portion of the line graph. As shown, the patient results illustrate that 94% of the population has a lower LDL particle value **42a**, 71% of the population has a higher large HDL value **43a**, and 78% of the population has a lower large VLDL trigylceride **44a** level.

In a preferred embodiment, the population values are based on scientific results obtained from subjects in the Framingham Offspring Study. *See* Wilson et al., *Impact of National Guidelines for Cholesterol Risk Factor Screening. The Framingham Offspring Study*, JAMA, 1989; 262: 41-44. Of course the values presently defined for the risk assessment **36**, **46** portion of the summary may change over time and more or alternate risk categories may be added. Further, the actual ranges or definitions associated with the risk category values of one or more of the lipid panels or subclass categories may change over time and the present invention is not intended to be limited thereto.

The order of the measured values **31a**, **32a**, **33a**, **34a**, **41a**, **42a**, **43a**, and **44a** may be alternately arranged in the summary report **10**. In addition, the layout of the results may be alternately oriented (such as in vertical segments). Of course,

the second segment **30** (lipid profile) or the third segment **40** (subclass profile) may be provided alone depending on a customer's specifications.

It is also preferred that the report include a discussion of "flagged" or potential increased risk factors identified by the subclass values **41a, 42a, 43a, 44a** as compared to predetermined risk assessment criteria. For example, as shown in **Figure 5**, a supplemental risk factor segment **50** can be included in the summary report **10'**. The supplemental segment can include a preliminary informational introduction **50a** which notes that coronary heart disease risk can significantly increase when there is a clustering of metabolic abnormalities not detected by standard lipid measurements. The supplemental risk segment **50** summarizes the presence of a metabolic profile associated with a higher level of risk than indicated by the LDL cholesterol value **32a**. In a preferred embodiment, the "clustering" is indicated by a mark **51a, 52a, 53a, 54a** in a corresponding subclass box **51b, 52b, 53b, 54b**.

As shown, this supplemental risk factor segment **50** includes a summary **50'** for subclass values indicating abnormalities which indicate increased risk, *i.e.*, Pattern B small LDL **51**, elevated number of LDL particles **52**, low level of large HDL **53**, and elevated level of large VLDL **54**. As shown, if the summary **50'** is selected (shown as positive with a "check mark" proximate to the category), then the CHD risk is increased. An informational guideline **51c, 52c, 53c, 54c**, for the abnormal values is positioned proximate to the subclass box.

In an alternative embodiment (not shown), a computer program can be configured to provide the analysis and risk assessment in a manner in which it can suppress non-abnormal results and provide only abnormal results in this segment **50'**. Thus, if a patient has two "abnormal" or elevated risk values associated with the subclass readings, then only those two subclasses will be printed on this segment **50** of the summary report **10**.

In any event, as indicated for the small LDL variable **51**, small LDL size (Pattern B) is a hallmark of the "atherogenic lipoprotein phenotype" and confers approximately a three-fold higher risk compared to the large LDL trait (Pattern A). There is evidence that suggests that small LDL particles may be inherently more

atherogenic than large LDL. As regards an elevated number of LDL particles **52** (shown as for a value corresponding to the upper 33% of the population), unlike LDL cholesterol, LDL particle concentration (related closely to plasma apo B level), may be the single best indicator of LDL-associated CHD risk and the best target of risk reduction therapy. *See* Lamarche et al., Circulation 1996; 94:273-278. The supplemental risk factor segment **50** can also indicate the presence of low levels of large HDL **43**. Low levels of large HDL **43** (shown as a value corresponding to the lower 33% of the population) may be a positive risk factor, as only larger HDL subclass particles appear to protect against CHD -- whereas small HDL may even be atherogenic. Therefore, large HDL, rather than total HDL cholesterol, may be a more sensitive risk factor. *See* Freedman et al., Arterioscler. Thromb. Vasc. Biol. 1998; 18:1046-53. Similarly, as shown, elevated levels of large triglyceride rich VLDL particles **54**, appear to be associated with coronary artery disease (CAD) severity, substantially independent of plasma triglycerides. High concentrations of large VLDL in fasting plasma may be a marker for delayed chylomicron clearance (postprandial lipemia).

As shown in **Figures 2** and **6**, the summary report **10** may also include a fifth segment **60** showing a graphical representation of the subclass levels provided by NMR analysis. Referring to **Figure 6**, the fifth segment **60** divides the information into three groups of subclasses, VLDL triglyceride subclasses **61**, LDL cholesterol subclasses **62**, and HDL cholesterol subclasses **63**. Each of the three subclasses **61**, **62**, **63** are further divided to graphically portray selected or grouped results. As shown, the VLDL triglyceride subclass **61** is divided into three groupings, a large VLDL subclass **61a** (shown with a concentration or value of 30), a medium VLDL subclass **61b** (shown with a value of 74), and a small VLDL subclass **61c** (shown with a value of 4). The LDL subclasses **62** shown in **Figure 6** include an IDL cholesterol subclass **62a** (shown with a value of 9), a large LDL cholesterol subclass **62b** (shown with a value of 31), a medium LDL cholesterol subclass **62c** (shown with a value of 15), and a small LDL cholesterol subclass **62d** (shown with a value of 110). The HDL subclasses shown are large HDL cholesterol **63a** (shown with a value of 21) and small HDL **63b** (shown with a

value of 21 For each subclass level shown **61a-c, 62a-d, 63a-b**, the level measured in mg/dL are provided in text form at the top of the respective bar. The height of the bar gives the percent of population with lower levels of the graphed value. Advantageously, the HDL cholesterol subclass grouping can visually indicate the breakdown of the constituents of the overall HDL class **33** (value 42) shown on the summary report **10** to indicate the correspondence between the two subclasses to the overall HDL number. As shown, the results indicate an even amount of small HDL cholesterol **63b** versus large HDL cholesterol **63a**. Of course, other groupings or different subclass information may be separated out such as the separable subclass information shown in **Figure 9**, as will be discussed further below.

The risk assessment report **10'** may also include a sixth segment **70** addressing the primary prevention risk assessment for an individual. Referring to **Figure 7**, the sixth segment **70** incorporates certain behavioral and medical background of an individual with the lipid profile and subclass values. For example, a patient's age, smoking history, blood pressure, LDL value **32** and HDL value **33**, and whether he or she has diabetes, and/or other risk pertinent information such as whether a blood relative has diabetes or CHD. A risk factor value is assigned to each of these parameters. Additionally, positive risk factors can be assigned a negative risk value (**Figure 7A**). Examples of positive risk factors include whether the patient actively exercises at least three days per week, has a high HDL cholesterol level **33a**, has a Pattern A LDL size **41a**, and has elevated levels of large HDL **43a**). The positive and negative risk factors can be added to yield an overall risk value. In any event, a percentage based predictive CHD risk is generated corresponding to the total calculated risk. A target norm for the patient's age and gender can also be provided. In a preferred embodiment, the relative "negative" risk factors and predictive analysis is generated as described by Wilson et al., in *Prediction of Coronary Heart Disease Using Risk Factor Categories*, May 12, 1998 (copyright 1998 American Heart Association, Inc.).

As also shown in **Figure 7**, the risk of coronary heart disease is presented in several different percentage-based risk evaluations. A first risk **76a** is as indicated by the risk point total. A second risk **76b** is a "desirable risk", i.e. the

risk associated a non-smoking, non-diabetic person of the same gender and age having optimal blood pressure (less than 120/80), LDL cholesterol of 100-129 mg/dL, and HDL cholesterol of 55mg/dL. A third risk **76c** is a "projected" risk to provide an age accounting balancing of risk (age typically being the single largest risk contributor as indicated in the risk factor chart). Thus, the third risk **76c** evaluation can help provide a helpful basis for managed care assessment. A fourth risk **76d** can also be included to provide a desirable risk at age 60 (one indicative of only age-related risk conditions). The age standard for persons under the 60 year mark can establish a more clear assessment of the risk a person with the measured values has for coronary heart disease. Advantageously, a patient may take more immediate steps to attempt to reduce the indicated exposure risk when presented with a longer-term standard reference risk.

The summary report **10"** may also include a seventh segment **80** which is directed toward secondary prevention guidelines. As shown in **Figure 8**, the sixth segment presents a discussion **80a** on special risk considerations for patients with established coronary heart disease, other atherosclerotic vascular disease, or diabetes. These patients are considered to be at particularly high risk as measured by the NCEP guidelines. For patients having one or more of these conditions, the present recommendations are lipid management to reduce LDL cholesterol to under 100 mg/dL. The corresponding NMR LDL particle concentration target is 1100 nmol/L. For patients with small LDL (Pattern B) and a clustering of the supplemental risk factors **50** discussed above, it can be especially important to reach these LDL goals. Smoking cessation, increased exercise, healthy diet, and blood pressure control can also be considered important treatment goals.

Figure 9 graphically illustrates some of the subclass information provided by NMR analysis according to the present invention. This graph also shows the present medical understanding of the relationship between various lipoprotein subclass levels and CHD risk. The plus signs represent a positive association with disease (larger size signs indicating subclasses conferring higher risk). The higher levels indicating a higher risk. The minus signs represent a negative association, higher levels equals a lower risk. In a preferred embodiment, certain of the

individual subclass information shown is combined with other subclass information shown to provide the subclass groupings described above for **Figure 6.**

As discussed above, a preferred embodiment of the summary report **10** includes portions of the subclass information shown in **Figure 8** (**42, 43, 44**) and also includes LDL size **41**. Of course, the summary report **10** can include other subclass information within the scope of this invention. Advantageously, the instant reporting system and product can be used to provide important patient-specific information in an easy to assess manner and can be generated on a mass commercial production basis. Of course, some or part of this information may be presented in a computer readable medium or hard or paper report.

Figure 10 illustrates a flow chart of methods, apparatus (systems) and computer program products according to the invention. It will be understood that each block of the flowchart illustration, and combinations of blocks in the flowchart illustrations, can be implemented by computer program instructions. These computer program instructions may be loaded onto a computer or other programmable data processing apparatus to produce a machine, such that the instructions which execute on the computer or other programmable data processing apparatus create means for implementing the functions specified in the flowchart block or blocks. These computer program instructions may also be stored in a computer-readable memory that can direct a computer or other programmable data processing apparatus to function in a particular manner, such that the instructions stored in the computer-readable memory produce an article of manufacture including instruction means which implement the function specified in the flowchart block or blocks. The computer program instructions may also be loaded onto a computer or other programmable data processing apparatus to cause a series of operational steps to be performed on the computer or other programmable apparatus to produce computer implemented process such that the instructions which execute on the computer or other programmable apparatus provide steps for implementing the functions specified in the flowchart block or blocks.

Accordingly, blocks of the flowchart illustrations support combinations of means for performing the specified functions and program instruction means for

performing the specified functions. It will also be understood that each block of the flowchart illustrations, and combinations of blocks in the flowchart illustrations, can be implemented by special purpose hardware-based computer systems which perform the specified functions or steps, or combinations of special purpose hardware and computer instructions.

As shown in **Figure 10**, lipoprotein measurement values are obtained from a patient or subject, the values include at least one subclass value (**Block 810**). Preferably, an NMR spectral analysis is performed on a blood plasma sample and the lipoprotein values measured include the major lipoprotein constituents (total cholesterol, HDL, LDL, and triglycerides) as well as selected subclass values. The patient specific at least one subclass value is compared to predetermined test criteria to determine whether the value is associated with a higher or lower risk of developing coronary heart disease (**Block 820**). Preferably, the test criteria employed for the lipoprotein results (including the lipoprotein subclass values) correspond to a defined level of risk (low to high) of developing CHD. Preferably, the predetermined test criteria are based on scientific target "norms" or population based norms associated with higher or lower risks of CHD. These values may change over time or can be alternately identified for patients with increased secondary risk factors.

For example, if a patient has established CHD, atherosclerotic vascular disease, and/or diabetes, the "risk" criteria and values of certain constituents or subclasses may be lowered on the summary report relative to a patient without said identified diseases such that a "high" risk value may be associated with a lower value (optional **Block 830**). This report's ability to automatically adjust or lower the risk value based on preexisting conditions can help alert the physician that this patient is subject to stricter lipid management or protocol by visually indicating the lower risk factor value targeted for this individual. Generally, the test criteria may be set in a controlled revision software format which can be updated as NCEP guidelines or current medical analysis updates risk related information or values.

As shown in **Figure 10**, the next step is to determine the level of risk associated with the lipoprotein subclass value(s) (*i.e.*, whether it is identified as

being associated with increased-risk (and/or reduced-risk) of developing coronary heart disease) (**Block 840**). The NMR spectroscopy measured lipoprotein results are presented with a risk category associated with the measured result visually enhanced in a two-dimensional window for easy recognition thereof (**Block 850**). The two-dimensional window can be a display section on a computer screen, display monitor, or electronic or hard copy or a commercial report portion or segment. Advantageously, the customized display or report can be automatically generated or mass produced such as at a commercial facility or laboratory. As shown in **Figure 1**, it is preferred that each of the risk analysis information associated with the measured value be presented such that the "high" or elevated risk information is visually enhanced and aligned along one side (the same side as the other risk information for the other values) of the report or display.

Optionally, as indicated by **Blocks 870, 875, 880** and **885**, additional risk assessment information can also be provided. For example, a supplemental risk assessment for selected abnormal or higher risk subclass results can be provided (**Block 870**). This supplemental risk assessment can customize the report to provide more detailed information regarding selected or grouped subclass variables (such as LDL size or particles, large HDL, and/or large VLDL triglycerides, or atherogenic dyslipidemia). Similarly, a subclass level risk assessment can provide a graphic and textual breakdown of certain subclass groupings or selected subclass data (**Block 875**).

Alternatively, or additionally, a primary prevention risk assessment prediction assessment can be provided based on risk factors assigned to one or more of behavioral, medical, and/or selected lipoprotein measured constituent and/or subclass values (**Block 880**). As another alternative or addition, a secondary prevention guideline corresponding to recognition of the patient's diagnosis with certain high-risk medical conditions can be provided (**Block 885**).

Preferably, the method of the instant invention subdivides the major lipoprotein constituents and the LDL pattern separately into at least three risk categories each. It is also preferred that, the LDL particles **42**, the large HDL value **43** and the large VLDL triglyceride value **44** are compared to a population based-

norm and a line graph illustrates the actual measured result compared to the population with higher or lower levels of the measured value.

The behavioral or medical input can be electronically input or input via a user at the lab or report site (for example, at a blood depository or lab where the blood or plasma sample is taken from a patient). It is typical that an identification number (bar-coded) is assigned to the vials for tracking. Accordingly, a hard copy or electronic data can also be identified such as with the same identification number. Once received at the central processing facility or NMR spectroscopy laboratory, the electronic data can be entered into the facility computer and matched with the lipoprotein measurements, and a customized patient profile summary report can be conveniently generated (either in one or more of soft or hard copy). In one embodiment, the summary report can be encrypted and emailed in electronic format to a physician's address for contemporaneous data reporting. Of course, the patient can be identified by a "permanent" number to track trend or drug therapy or other treatment impact over time. Additionally, a data base can be kept to analyze population trends (age, location, etc., versus one or more of the identified risk factors represented by a subclass and/or constituents) to provide important indicators of the population for medical use.

In an additional preferred embodiment (shown in **Figure 11**) a summary report **10'''** (shown as the coronary heart disease report) is similar in some respects to the summary reports **10, 10'** discussed above. In this embodiment, the second segment **30'** is a lipid profile that provides lipid profile values which are determined by measuring plasma lipoprotein levels directly by NMR, then converting concentrations to cholesterol or triglyceride units assuming that each lipoprotein has a normal lipid composition as will be appreciated by one of skill in the art. For most patients, NMR and standard lipid panel values will closely agree. Patients with certain metabolic abnormalities or elevated triglycerides may have cholesterol-depleted LDL. In these cases LDL concentrations determined by NMR may likely be higher than those inferred by conventional or standard LDL cholesterol tests.

In this embodiment, the lipid profile segment **30'** includes total cholesterol **31**, LDL concentration **32'** (cholesterol equivalents), HDL concentration **33'**(cholesterol equivalents), and triglycerides **34**. Again, each of the associated values **31a'**, **32a'**, **33a'**, and **34a'** are accentuated such as by positioning them in aligned order in a respective adjacent box **31b**, **32b**, **33b**, and **34b**, respectively. Further, each of the values is preferably horizontally aligned with at least three risk categories **36**, the risk category associated with the determined value being accentuated for ease of reference as discussed above. Preferably, the risk categories are predetermined to correspond to the current NCEP risk categories. For example, "high" risk category generally represents a value which is >80% of the population. Similarly, the intermediate or borderline risk range is above 50% and 80% or below, while the desirable risk range is 50% or below.

As shown, it is also preferred that the LDL concentration **32'** include four risk categories, the fourth **36d'** being an "optimal" value for secondary prevention (preferably set to a target value which is at a value of 20% or below the general population). This secondary prevention guideline is directed toward patients with established coronary heart disease, diabetes, or other atherosclerotic diseases as discussed above. Thus, this secondary guideline or "optimal" risk visual illustration can remind a treating physician of the reduced target value and can also facilitate a visible reminder for the patient, each of which can keep the secondary reduction target in the forefront of patient counseling thereby facilitating ongoing monitoring and reinforcing the importance of aggressive therapy (behavioral changes or other remediation) for a high-risk patient. This optimal box **36d'** can be automatically accentuated in "red-line" or other accent as appropriate (such as via patient history data input) to remind the patient and/or physician that the patient is identified as a patient meeting the criteria for this target value reduction. Thus, for example, for a patient with diabetes, the LDL concentration risk categories **36** may bold or accent two-risk boxes, the "optimal" box with no value (for cases where a patient's result is above this value) and the actual risk box indicating the patient's actual value (not shown). Alternatively, the optimal box **36d'** can be

programmed in the computer generated report to be suppressed on a non-relevant patient's report (also not shown).

As is also shown in **Figure 11**, the report **10'''** preferably also includes a third segment **40'** which is a subclass profile providing predetermined lipoprotein constituent results. As shown, the subclass profile includes, in longitudinal serial order, LDL particles **42'**, LDL size **41'**, large HDL (cholesterol) **43'**, and large VLDL (triglyceride) **44'**.

Preferably, this subclass profile segment **40'** is configured to mirror the lipid profile (second segment **30'**) listed constituent order (for easier cross-reference). Thus, as shown, a patient with a borderline reading on the LDL concentration value **32'** (borderline risk) can then refer to the below listed subclass profile and note that the NMR measurement breakdown of the LDL concentration value **32a'** really indicates that he or she is high risk both in LDL particles **42'** and LDL size **41'**. Similarly, the HDL concentration **33'** referenced to the large HDL cholesterol **43'** indicates a good correspondence (the large HDL being less than 18). Again, the risk categories for LDL particle concentration categories in the subclass profile **40'** are set to correspond to the NCEP risk categories for LDL cholesterol (on a percentile equivalence basis) and can provide a constructive alternate target for therapy consideration or monitoring purposes (preferably, the risk percentages for each of the categories are about as shown, *i.e.*, optimal 20%, desirable 50%, borderline/intermediate 80% or below (and above 50%), and high risk as above 80% of the population based on the Framingham study discussed above. The large HDL is the protective component of HDL and levels below the 20th percentile (less than about 18 mg/dL) indicate higher risk (positive risk factor) while levels above the 80th percentile (greater than about 42 mg/dL) indicate lower risk (negative risk factor). Elevations of large VLDL are related to delayed chylomicron clearance and higher CHD risk, and preferably, values above the 80th percentile (greater than about 33 mg/dL) define the "higher-risk" category. **Figure 11A** illustrates the summary report **10'''** with a modified subclass profile **401**. As shown, the LDL particle constituent has been labeled "LDL Particle

Concentration" **42''** and the adjacent text block **402** includes values associated with the particular percentile reference.

In contrast to the first embodiment discussed above, these summary reports **10'''** present the subclass profile as a segmented risk analysis presentation format **146** (rather than a risk percentage continuum). Preferably, the segment format **146** is configured to mirror that of the lipid profile **30'**. That is, the risk characterization includes the same number of risk categories with the increased, positive, or high-risk category all being positioned to one side of the presentation format. Thus, a patient or physician can readily discern the risk category associated with the NMR results (preferably, the high-risk categories are all aligned along the right hand side of the report). As for the lipid profile section **30'**, the results are preferably presented in a visually enhanced format, with each of the specific lipoprotein results **42a'**, **41a'**, **43a'**, and **44a'** being presented in a box **42b'**, **41b'**, **43b'**, and **44b'**.

Stated differently, it is readily apparent at a glance that the patient with the NMR measurements provided in **Figures 11** or **11A**, has a high-risk subclass profile **40'** but only a single positive risk factor associated with the lipid profile panel **30'**. In practice, without a NMR subclass profile, a patient with this type of lipid profile may have been overlooked as a candidate for further review or potential behavior altering counseling (or even drug therapy) because of the number of borderline lipid measurement results. Preferably, as stated above, the actual numerical result is presented alongside the lipoprotein constituent while the risk categories associated therewith are horizontally oriented with the risk associated with the actual numerical result highlighted to indicate the risk level associated with that lipoprotein result.

Figure 12 illustrates a preferred embodiment of a technical report **100** associated with NMR measured lipoprotein constituents. In order to provide a more representative indication of a patient's risk, it is desirable to provide an automatically (or semi-automatically) computer generated coronary heart disease (CHD) risk assessment module **150** as a portion of the lipid panel analysis (or even as a separate evaluative report). Preferably, the CHD risk assessment module

includes two key identifiers **151, 152**. The first key identifier **151** is analyzing whether the patient's LDL particle number is elevated compared to a predetermined level. Preferably, the predetermined elevated level is set at a value which is approximately equivalent to the upper 50% of the population (greater than about 1400 nmol/L). The module **150** also preferably includes the relevant risk test measurement positioned adjacent to the particular constituent **151a, 153a, 154a, 155a**. This elevated LDL particle number **151** is a key identifier of coronary heart disease risk, and indeed, may be the single best indicator of LDL-associated CHD risk. *See Generally*, Lamarche et al., Circulation, 1996; 94:273-278. Of course, the "elevated" target value could be set at above 50%.

The second key identifier **152** is termed "atherogenic dyslipidemia". As used herein, the term "atherogenic dyslipidemia" refers to an increased risk of CHD based on a clustering or confluence of NMR measured lipoprotein constituent or subclass abnormalities. Preferably, the presence or absence of atherogenic dyslipidemia is determined based on a predetermined level of at least three different NMR lipoprotein subclass or constituent values. In the past, the presence of elevated triglycerides has been used as a proxy to indicate the atherogenic dyslipidemia condition while plasma apo B protein level measurement techniques have been used to estimate the number of LDL particles. However, and advantageously, the NMR based lipoprotein measurements can provide more detailed, easier, and commercially reproducible lipoprotein component measurements. Using certain of these NMR component measurements individually (such as the determination of an elevated number of LDL particles) and in combination (to determine the presence of a clustering of abnormalities) can, thus, provide an easier and more reliable determination and assessment of a patient's risk for CHD.

In a preferred embodiment, the positive or affirmative match to test criteria for at least two of the three selected-lipoprotein subclass or constituent values results in a designation of atherogenic dyslipidemia. This NMR-based lipoprotein atherogenic dyslipidemia test criteria **152** can provide a more reliable analysis of a patient's risk for CHD over isolated component values. For example, a patient's

individual or component constituent or subclass values may all be insufficient to determine or provide a reliable indication of increased risk of CHD, but a clustering of certain abnormal conditions or results can indicate a higher-risk metabolic condition. Indeed, patients with a clustering of the lipoprotein subclass abnormalities shown (small LDL 153, low level of HDL 154, and elevated level of large VLDL 155) are at higher risk of CHD when risk identifier 151 is indicated, *i.e.*, when LDL particle numbers are elevated. Thus, the present invention uses positive matches for two or more of the plurality of lipoprotein constituent values listed to indicate the presence of the higher-risk metabolic condition.

The CHD atherogenic dyslipidemia assessment preferably includes a test for small LDL 153 and low levels of large HDL 154. Small LDL 153 (Pattern B) is a hallmark of atherogenic dyslipidemia and confers about a three-fold higher risk compared to the large LDL trait (Pattern A). Evidence suggests that small LDL particles may be inherently more atherogenic than large LDL. An indication of a low level of large HDL 154 has a positive association with CHD. A low level of large HDL means a NMR derived value which is below the 50%, and more preferably means the value is below 35% (less than about 23 mg/dL). That is, only the larger HDL subclasses appear to be protective, whereas small HDL is positively associated with CHD. Therefore, large HDL, rather than total HDL cholesterol, may be a more sensitive risk factor and, indeed, an independently predictive marker for CHD in addition to being a factor which can assist in the determination of atherogenic dyslipidemia.

Similarly, the CHD atherogenic dyslipidemia risk assessment preferably includes a test for elevated levels of large VLDL 155. Elevated levels of large, triglyceride-rich VLDL particles have been associated with the severity of CAD, independently of plasma triglycerides. High concentrations of large VLDL in fasting plasma are a marker for delayed chylomicron clearance (postprandial lipemia). "Elevated" for VLDL means the value is in the upper 50th percentile, and preferably means above about the 65th percentile (greater than about 17 mg/dL) or such as in the upper 33%.

Additional or alternative lipoprotein subclass or constituent parameters may also be used as a test parameter for atherogenic dyslipidemia. Similarly, the percentile-based values are preferably as shown but may also be other values. For example, these values can be altered to reflect contemporary guidelines by the NCEP or other health organization, statistically valid tests or studies, scientific or empirical data and the like. As will be appreciated by one of skill in the art, the percentile values are preferably set to reflect an acceptable sensitivity/specificity test result. **Figure 12A** illustrates another embodiment with a modified risk assessment module **150'**. As shown, the first key risk factor **151** is labeled "Elevated LDL Particle Conc.[entration]". The module **150'** includes a modified test criteria over that in **Figure 12** and also includes values rather than percentile references. The text in certain of the associated risk analysis is also modified from **Figure 12**.

The population percentile values described herein are from NMR data obtained from analysis of 3,437 subjects in the Framingham Offspring study. However, the present invention is not limited thereto. As noted above, these values may change over time, or other percentiles or values may be used.

As discussed for the report of **Figure 2**, the reports **100** shown in **Figures 12** and **12A** also preferably include a subclass graphic analysis segment **60'** with grouped subclass data. As shown, the HDL results give a visual representation of the disparity of small (bad or harmful) HDL to the large (good) HDL. This patient is above the 75th percentile in (bad) small HDL and indeed has a positive risk indication across the spectrum of the lipoprotein subclass values (ignoring the low level of large HDL). Thus, this patient's overall conventional lipid profile is not reflective of his or her actual risk.

Figure 13 illustrates a hybrid summary report **110** with a subclass profile segment as shown in **Figure 11A** and a CHD risk assessment module as shown in **Figure 12A**. This report **110** provides an easy to read single page overview or summary of the most relevant heart-specific test measurement results.

Figure 14 schematically illustrates a system according to one embodiment of the present invention. As shown, the system includes an NMR measurement

apparatus **500** for measuring the lipoprotein constituents of a patient's blood or plasma sample. A suitable method for determining the lipoprotein constituents is disclosed in U.S. Patent No. 4,933,844 to Otvos, entitled "*Measurement of Blood Lipoprotein Constituents by Analysis of Data Acquired From an NMR Spectrometer*" and U.S. Patent No. 5,343,389 to Otvos, entitled "*Method and Apparatus for Measuring Classes and Subclasses of Lipoproteins*", incorporated by reference above. The system also includes a computer means for generating an automatic lipoprotein report and determining CHD risk based on the NMR measured constituent values **525**. The computer means then generates a customized lipoprotein report which includes information identifying the CHD risk attendant with the NMR derived lipoprotein constituent values **530**. Preferably, the system is operably associated with a peripheral device such as another computer or internet or printer so as to transmit and print or display the customized report.

As will be appreciated by one of skill in the art, the present invention may be embodied as a method, data processing system, hard copy two-dimensional printed material report, computer screen display, or computer program product. Accordingly, the present invention may take the form of an entirely hardware embodiment, an entirely software embodiment or an embodiment which combines software and hardware aspects. Furthermore, the present invention may take the form of a computer program product on a computer readable storage medium having computer readable program code means embodied in the medium. Any suitable computer readable medium may be utilized including for example, hard disks, CD-ROMs, optical storage devices, or magnetic storage devices.

A portion of the disclosure of this patent document contains material which is subject to copyright protection. The copyright owner, LipoMed, Inc., of Raleigh, North Carolina, has no objection to the facsimile by anyone of the patent document or the patent disclosure, as it appears in the Patent and Trademark Office patent file or records, but otherwise reserves all rights whatsoever.

The foregoing is illustrative of the present invention and is not to be construed as limiting thereof. Although a few exemplary embodiments of this invention have been described, those skilled in the art will readily appreciate that

many modifications are possible in the exemplary embodiments without materially departing from the novel teachings and advantages of this invention. Accordingly, all such modifications are intended to be included within the scope of this invention as defined in the claims. In the claims, means-plus-function clauses are intended to cover the structures described herein as performing the recited function and not only structural equivalents but also equivalent structures. Therefore, it is to be understood that the foregoing is illustrative of the present invention and is not to be construed as limited to the specific embodiments disclosed, and that modifications to the disclosed embodiments, as well as other embodiments, are intended to be included within the scope of the appended claims. The invention is defined by the following claims, with equivalents of the claims to be included therein.

THAT WHICH IS CLAIMED IS:

1. A computer program product for generating personalized lipoprotein-based information, the computer program product comprising:

a computer readable storage medium having computer readable program code means embodied in said medium, said computer-readable program code means comprising:

computer readable program code means for generating NMR-based lipoprotein measurement values for a patient's blood sample, the lipoprotein measurement values including at least one subclass variable value;

computer readable program code means for comparing the at least one patient lipoprotein subclass variable value with predetermined test criteria for determining whether the at least one subclass variable value is associated with a higher or lower risk of developing coronary heart disease;

computer readable program code means for identifying, for the at least one measured subclass variable value, the corresponding risk level associated with coronary heart disease; and

computer readable program code means for providing a risk analysis portion adjacent the measured lipoprotein values, the risk analysis portion displaying information related to a range of values and corresponding to higher and lower coronary heart disease risk, wherein the measured value is visually enhanced in the risk analysis portion to visibly indicate the level of risk associated therewith to thereby provide a contemporaneous reference guideline for interpretation of the measured value.

2. A computer program product according to Claim 1, wherein the computer readable program code means recognizes the measured lipoprotein values to include the major lipoprotein constituents of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides, and the subclass values associated with LDL size, LDL particles, large LDL cholesterol, and large VLDL triglyceride.

3. A computer program product according to Claim 1, further comprising computer readable program code means for presenting the lipoprotein measurement values such that each of the lipoprotein measurement values is substantially aligned.

4. A computer program product according to Claim 1, wherein the lipoprotein measurement values includes the major lipoprotein constituents of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides, and wherein the risk analysis portion subdivides the values associated with major lipoprotein constituents into at least three risk categories.

5. A computer program product according to Claim 1, wherein the computer readable program code means provides LDL size test criteria in a manner which identifies the LDL size as one of Pattern A, Pattern AB, and Pattern B.

6. A computer program product according to Claim 4, wherein the computer readable program code means visually presents the LDL size such that Pattern A is associated with lower risk and Pattern B is associated with higher risk.

7. A computer program product for personalized lipoprotein-based information, the computer program product comprising:

a computer readable storage medium having computer readable program code means embodied in said medium, said computer-readable program code means comprising:

computer readable program code means for generating NMR-based lipoprotein measurement values for a patient's blood sample, the lipoprotein measurement values including at least one subclass variable value;

computer readable program code means for comparing the at least one patient lipoprotein subclass variable value with predetermined test criteria for determining whether the at least one subclass variable value is associated with a higher or lower risk of developing coronary heart disease;

computer readable program code means for identifying, for the at least one measured subclass variable value, the corresponding risk level associated with coronary heart disease;

computer readable program code means for providing a risk analysis portion adjacent the measured lipoprotein values, the risk analysis portion displaying information corresponding to higher and lower coronary heart disease risk, wherein the measured value is visually enhanced in the risk analysis portion to visibly indicate the level of risk associated therewith to thereby provide a contemporaneous reference guideline for interpretation of the measured value; and

computer readable program code means for comparing a plurality of the NMR-based lipoprotein measurement values to predetermined test criteria to determine the presence or absence of atherogenic dyslipidemia.

8. A computer program product according to Claim 7, wherein the NMR-based lipoprotein values include the major lipoprotein constituents of total cholesterol, LDL concentration in cholesterol equivalents, HDL concentration in cholesterol equivalents, and triglycerides, and the subclass values associated with LDL size, LDL particles, large HDL cholesterol, and large VLDL triglyceride.

9. A computer program product according to Claim 8, further comprising computer readable program code means for presenting the lipoprotein measurement values such that each of the lipoprotein measurement values is substantially aligned.

10. A computer program product according to Claim 8, wherein the risk analysis portion for each of LDL concentration in cholesterol equivalents and LDL particles is divided into four different risk categories, and wherein the remainder of the risk analysis portions is divided into three discrete segment risk categories.

11. A computer program product according to Claim 8, wherein the computer readable program code means for comparing a plurality of the NMR-

based lipoprotein measurement values to predetermined test criteria to determine the presence or absence of atherogenic dyslipidemia includes comparing the measurement values to predetermined test criteria to determine the presence of small LDL, a low level of large HDL, and an elevated level of large VLDL, whereby the determination is made based on the positive test criteria match of at least two of the conditions.

12. A computer program code means according to Claim 9, wherein said computer readable program code means for the risk analysis portion includes a computer readable program code means for presenting a plurality of said subclass values as a series of horizontally extending discrete bar segments which graphically represents the subclass value relative to low to high risk.

13. An automated lipoprotein report which is generated at a commercial laboratory based on data corresponding to NMR-derived measurements, said report comprising a subclass profile segment comprising a plurality of patient-specific NMR derived lipoprotein constituent values, each constituent value having an adjacently positioned associated risk analysis portion which visually identifies the value with one of at least three discrete risk categories corresponding to a coronary heart disease risk level associated with said NMR-derived measurement value.

14. A lipoprotein subclass report according to Claim 13, wherein said subclass profile segment includes the NMR-derived value for LDL size, and wherein said associated risk analysis portion presents said LDL size value as one of: Pattern A corresponding to lower risk, Pattern B corresponding to higher risk, and Pattern AB corresponding to an intermediate risk; and wherein said LDL size value is identified in said risk analysis portion by visually enhancing the respective risk category associated with the patient-specific LDL value.

15. A lipoprotein report according to Claim 13, said NMR-derived lipoprotein constituent value includes LDL particle concentration, and wherein said corresponding risk analysis portion includes a risk category associated with a

desirable concentration level, a risk category associated with a borderline-high level, and a risk category associated with an increased or higher risk level, and a risk category associated with an optimal level corresponding to a goal for secondary prevention.

16. A method for assessing a patient's risk of coronary heart disease based on personalized NMR measured lipoprotein-based information, comprising the steps of:

generating NMR-based lipoprotein measurement values for a patient's blood plasma or serum sample, the NMR-based lipoprotein measurement values comprising a plurality of lipoprotein constituent values including a constituent value for LDL particle concentration;

comparing the LDL particle concentration with predetermined test criteria for determining whether the LDL particle concentration is elevated;

comparing a plurality of NMR-based lipoprotein constituent values to predetermined test criteria to determine the presence of atherogenic dyslipidemia; and

assessing a patient's risk of coronary heart disease based on the presence of at least one of an elevated LDL particle concentration and the determination of atherogenic dyslipidemia.

17. A method according to Claim 16, wherein the NMR based lipoprotein constituent values include the major lipoprotein constituents of total cholesterol, LDL concentration in cholesterol equivalents, HDL concentration in cholesterol equivalents, and triglycerides, and wherein the measured lipoprotein constituent values also include the values associated with LDL size, LDL particles, large HDL cholesterol, and large VLDL triglyceride.

18. A method according to Claim 16, wherein the NMR based lipoprotein constituent values used to determine the presence of atherogenic dyslipidemia lack a LDL particle concentration value.

19. A method according to Claim 16, wherein the predetermined test criteria for determining the presence of an elevated number of LDL particles is set at a value which is in about the upper 50% of the population.

20. A method according to Claim 16, wherein said step of comparing a plurality of NMR-based lipoprotein constituent values comprises comparing the NMR based values associated with LDL size, large HDL cholesterol, and large VLDL triglyceride to respective predetermined test criteria.

21. A method according to Claim 20, wherein the LDL size predetermined test criteria identifies the LDL size as Pattern B.

22. A method according to Claim 20, wherein the large HDL cholesterol predetermined test criteria identifies a low level of large HDL.

23. A method according to Claim 20, wherein the large VLDL triglyceride test criteria identifies an elevated level of large VLDL.

24. A method according to Claim 20, wherein said comparing step used to identify the presence of atherogenic dyslipidemia identifies the patient as having this condition based on a positive test match for at least two of the identified NMR based lipoprotein constituent values.

25. A method according to Claim 20, wherein the LDL size predetermined test criteria identifies the LDL size as Pattern B, the large HDL cholesterol predetermined test criteria identifies a low level of large HDL, and the large VLDL triglyceride test criteria identifies an elevated level of large VLDL, and wherein the presence of atherogenic dyslipidemia is determined based on the positive identification of at least two of the NMR lipoprotein based constituent values to predetermined test criteria.

26. A method according to Claim 16, wherein a low level of large HDL is used as an independently predictive factor to assess a patient's risk for coronary heart disease.

27. A method for providing personalized lipoprotein-based information, comprising the steps of:

generating NMR-based lipoprotein measurement values for a patient's blood plasma or serum sample, the lipoprotein measurement values including at least one subclass variable value;

comparing the at least one patient lipoprotein subclass variable value with predetermined test criteria for determining whether the at least one subclass variable value is associated with a higher or lower risk of developing coronary heart disease;

identifying what level of risk is associated with the at least one measured subclass variable value;

presenting the lipoprotein measurement values in a two dimensional window such that each of the lipoprotein measurement values are visually enhanced; and

providing a risk analysis portion adjacent the measured lipoprotein values, the risk analysis portion displaying information related to a range of values which correspond to higher and lower coronary heart disease risk, wherein the measured value is visually enhanced in the risk analysis portion to indicate the level of risk associated therewith to thereby provide a contemporaneous reference guideline for interpretation of the measured value.

28. A method according to Claim 27, wherein the measured lipoprotein values include the major lipoprotein constituents of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides, and wherein the measured lipoprotein values include the values associated with LDL size, LDL particles, large LDL cholesterol, and large VLDL triglyceride.

29. A method according to Claim 27, wherein the lipoprotein measurement values measure the major lipoprotein constituents of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides, and wherein the risk analysis portion subdivides the values associated with major lipoprotein constituents into at least three risk categories.

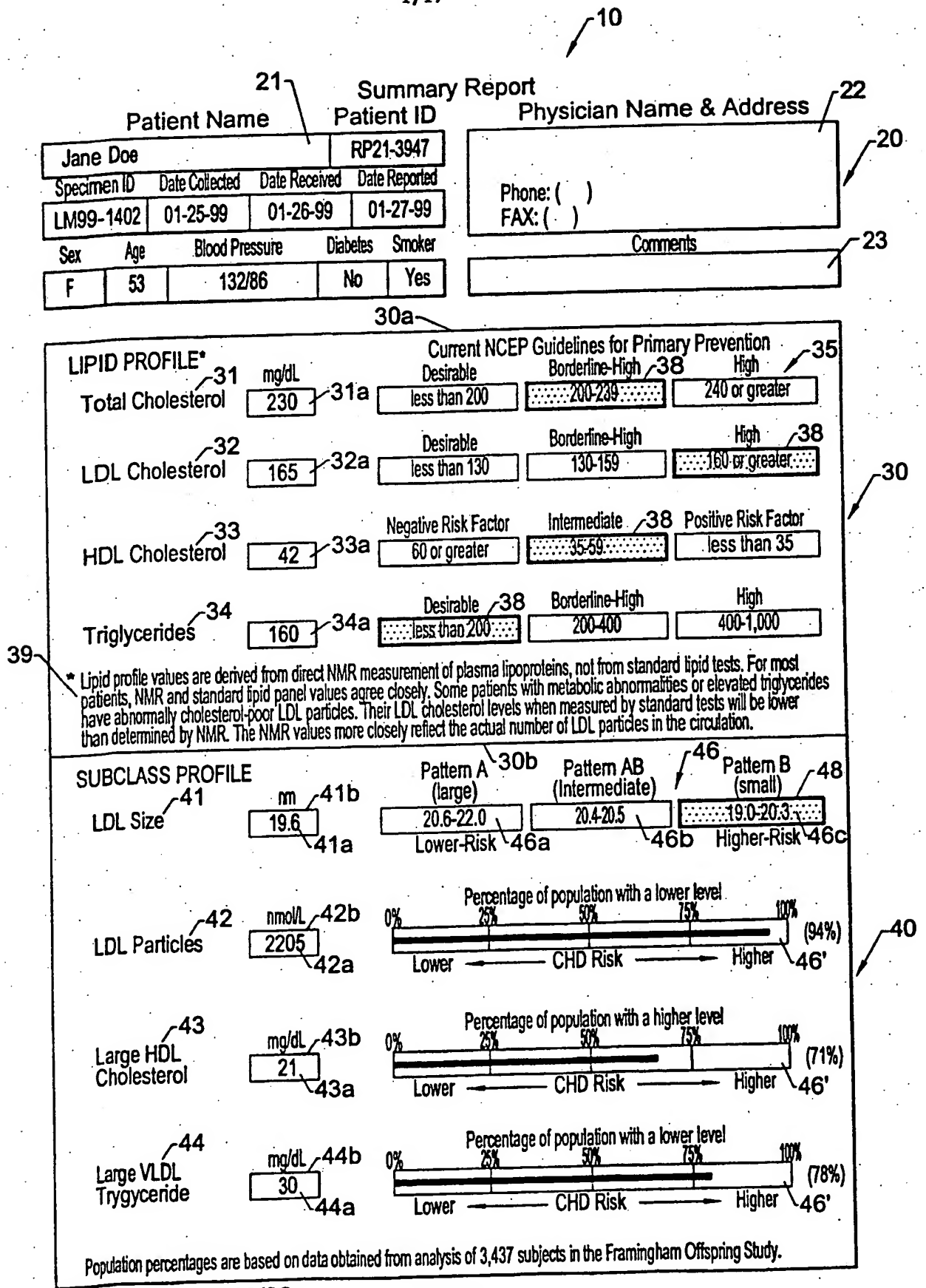


FIG. 1.

10'

Risk Assessment Report

20

Patient Name	Specimen ID	Date Reported
Jane Doe	LM99-1402	01-27-99

Supplemental Risk Factors

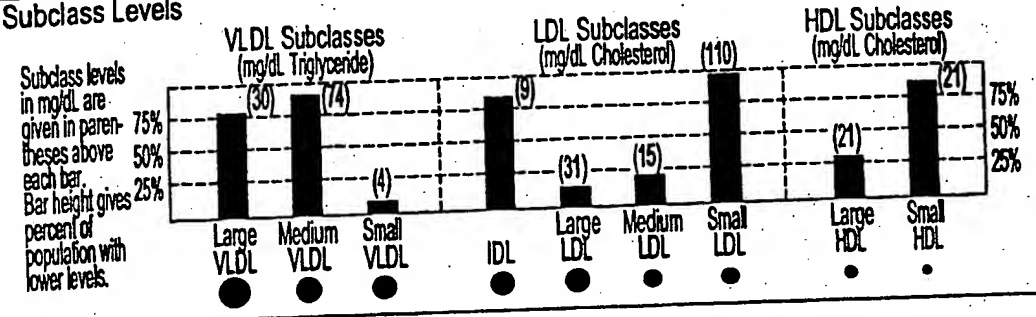
CHD risk can increase significantly when there is a clustering of metabolic abnormalities not detected by standard lipid tests. A check mark in multiple boxes below suggests the patient has a metabolic profile associated with a higher level of risk.

50

Small LDL	Pattern B ✓	Small LDL (Pattern B) is a hallmark of the "atherogenic lipoprotein phenotype" and confers about 3 to 4-fold higher risk compared to the large LDL trait (Pattern A). Evidence suggests that small LDL particles may be inherently more atherogenic than large LDL.
Elevated Number of LDL Particles	Upper 33% ✓	Unlike LDL cholesterol, LDL particle concentration (related closely to plasma apo B level), may be the single best indicator of LDL-associated CHD risk (Lamarche et al., Circulation 1996;94:273-278) and the best target of risk reduction therapy.
Low Level of Large HDL	Lower 33% ✓	Only the larger HDL subclasses appear to be protective, whereas small HDL is positively associated with CHD (Freedman et al., Arterioscler Thromb Vasc Biol. 1998;18:1046-53). Large HDL, rather that total HDL cholesterol, may thus be a more sensitive risk factor.
Elevated Level of Large VLDL	Lower 33% ✓	Elevated levels of large, triglyceride-rich VLDL particles have been associated with CAD severity, independently of plasma triglycerides. High concentrations of large VLDL in fasting plasma may be a marker for delayed chylomicron clearance (postprandial lipemia).

Subclass Levels

60



Primary Prevention Risk Assessment

Employs the Framingham algorithm in Circulation 1998;97:1837-1847

70

Given below is the patient's Framingham risk score and the estimated 10-year risk of developing CHD. Also given is the desirable low-level risk for the same age. Risk reduction should focus on modifying the starred risk factors.

71

Risk Factor Chart

Risk Factor	Relative Risk	Points
Age (53)		6
* LDL-C (165)	High	2
* HDL-C (42)	High	2
Blood Pressure (132/86)	Moderate	0
Diabetes (No)	Low	0
* Smoker (Yes)	High	2
	Point Total	12

Risk of Coronary Heart Disease

Point Total	10-Year CHD Risk	Point Total	10-Year CHD Risk	Point Total	10-Year CHD Risk
≤-2	1%	6	6%	12	15%
-1,0,1	2%	7	7%	13	17%
2	3%	8	8%	14	20%
3	3%	9	9%	15	24%
4	4%	10	11%	16	24%
5	5%	11	13%	≥17	≥32%

72

Patient's Risk 15% *Projected Risk at Age 60* 20%

Desirable Risk 6% *Desirable Risk at Age 60* 8%

73

Desirable risk is calculated for a non-smoking, non-diabetic woman the same age, with optimal blood pressure (<120/80), LDL cholesterol 100-129 mg/dL, and HDL cholesterol 55 mg/dL. Projected risk at age 60 assumes patient's risk factors do not change.

FIG. 2.

10"

Risk Assessment Report

20

Patient Name	Specimen ID	Date Reported
John Doe	LM99-3201	01-27-99

Supplemental Risk Factors

CHD risk can increase significantly when there is a clustering of metabolic abnormalities not detected by standard lipid measurements. Check marks in multiple boxes signify the presence of a metabolic profile associated with a higher level of risk than indicated by the LDL cholesterol value.

Small LDL	Pattern B ☑	Small LDL (Pattern B) is a hallmark of the "atherogenic lipoprotein phenotype" and confers approximately 3-fold higher risk compared to the large LDL trait (Pattern A). Evidence suggests that small LDL particles may be inherently more atherogenic than large LDL.
Elevated Number of LDL Particles	Upper 33% ☑	Unlike LDL cholesterol, LDL particle concentration (related closely to plasma apo B level), may be the single best indicator of LDL-associated CHD risk (Lamarche et al., Circulation 1998;94:273-278) and the best target of risk reduction therapy.
Low Level of Large HDL	Lower 33% ☑	Only the larger HDL subclass particles appear to protect against CHD, whereas small HDL may even be atherogenic (Freedman et al., Arterioscler Thromb Vasc Biol. 1998;18:1048-53). Large HDL, rather than total HDL cholesterol, may thus be a more sensitive risk factor.
Elevated Level of Large VLDL	Upper 33% ☑	Elevated levels of large, triglyceride-rich VLDL particles appear to be associated with CAD severity, independently of plasma triglycerides. High concentrations of large VLDL in fasting plasma may be a marker for delayed chylomicron clearance (postprandial lipemia).

50

Primary Prevention Risk Assessment

Employs the Framingham algorithm in *Circulation* 1998;97:1837-1847

Given below is the patient's Framingham risk score, the estimated absolute 10-year risk of developing CHD, and the desirable risk level for the same age. Risk reduction should focus on modifying the starred risk factors.

70

Risk Chart

71

Risk Factor	Relative Risk	Points
Age (46)		2
* LDL-C (198)	Very High	2
* HDL-C (41)	High	1
* Blood Pressure (135/91)	High	2
Diabetes (No)	Low	0
* Smoker (Yes)	High	2
	Point Total	9

Absolute 10-Year CHD Risk

72

Point Total	10-Year CHD Risk	Point Total	10-Year CHD Risk
≤-3	1%	6	11%
-2	2%	7	14%
-1	2%	8	18%
0	3%	9	22%
1	4%	10	27%
2	4%	11	33%
3	5%	12	40%
4	7%	13	47%
5	9%	≥14	≥56%
Desirable Risk for Same Age			4%

The desirable risk is calculated for a non-smoking, non-diabetic man the same age, with optimal blood presure (<120/80), LDL cholesterol 100-129 mg/dL, and HDL cholesterol 45 mg/dL.

73

Secondary Prevention Guidelines

Patients with established CHD, other atherosclerotic vascular disease, or diabetes are considered to be at particularly high risk by the NCEP. The primary goal of lipid management should be the reduction of LDL cholesterol to under 100 mg/dL. The corresponding NMR LDL particle concentration target is 1100 nmol/L. For patients with a small LDL (pattern B) and a clustering of the supplemental risk factors shown above, it is especially important to reach these LDL goals. Smoking cessation, increased exercise, healthy diet, and blood pressure control are also important treatment goals.

80

FIG. 2A.

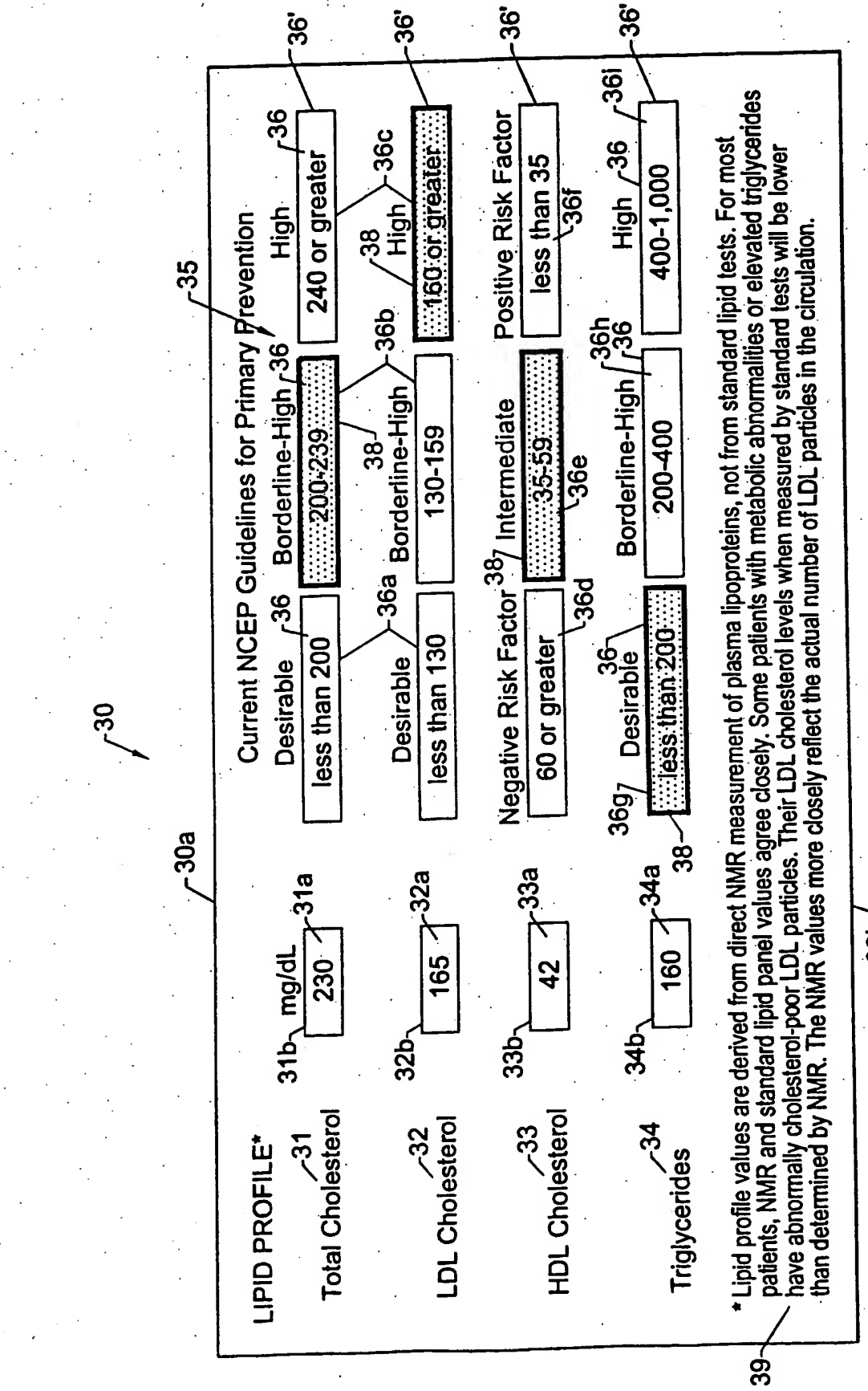

30
35
30a
30b
39
Current NCEP Guidelines for Primary Prevention
LIPID PROFILE*
Total Cholesterol
LDL Cholesterol
HDL Cholesterol
Triglycerides
mg/dL
Desirable
Borderline-High
High
Negative Risk Factor
Intermediate
Positive Risk Factor
less than 200
200-239
240 or greater
less than 130
130-159
160 or greater
60 or greater
35-59
less than 35
less than 200
200-400
400-1,000
230
165
42
160
* Lipid profile values are derived from direct NMR measurement of plasma lipoproteins, not from standard lipid tests. For most patients, NMR and standard lipid panel values agree closely. Some patients with metabolic abnormalities or elevated triglycerides have abnormally cholesterol-poor LDL particles. Their LDL cholesterol levels when measured by standard tests will be lower than determined by NMR. The NMR values more closely reflect the actual number of LDL particles in the circulation.

FIG. 3.

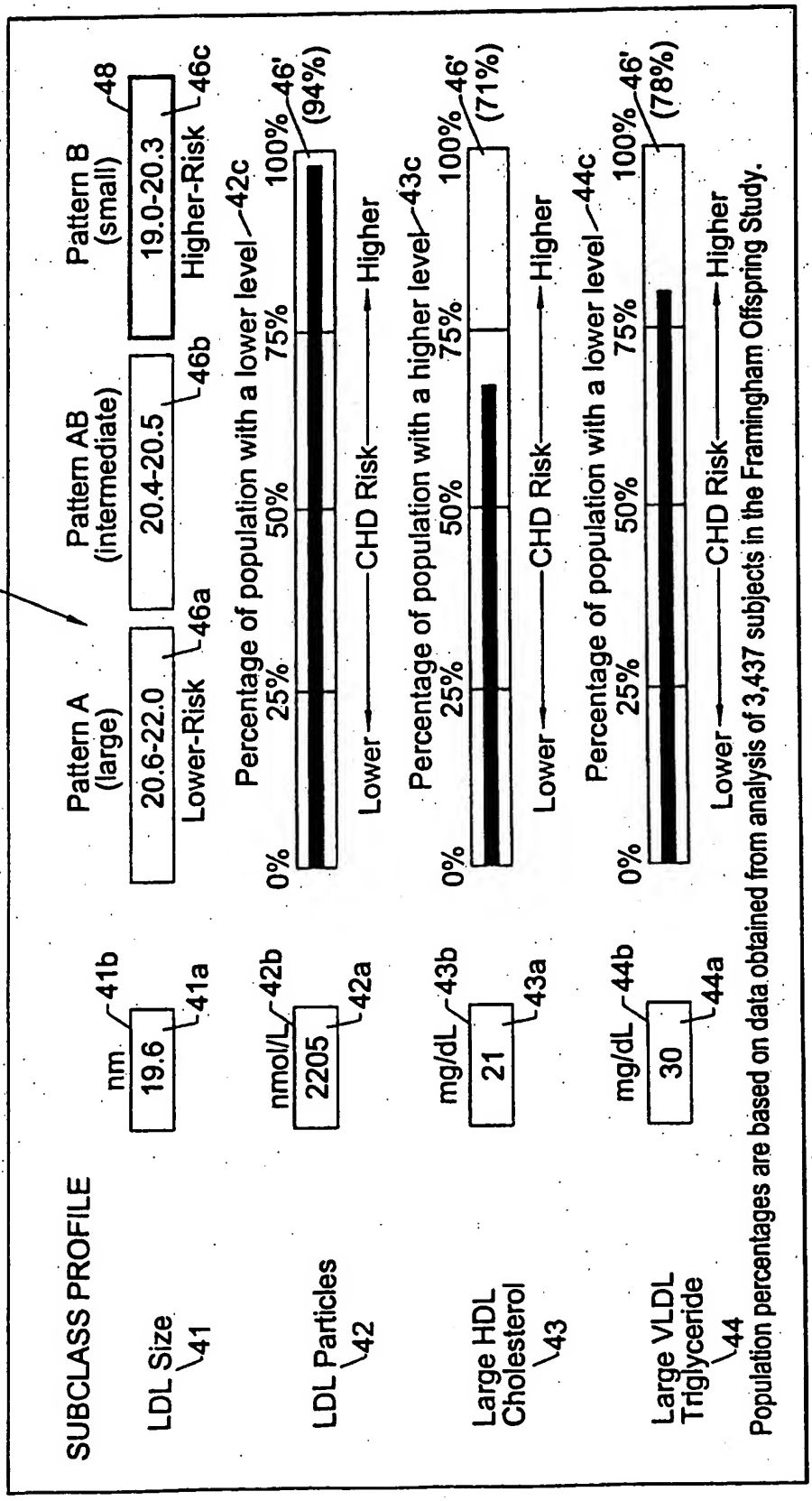

40
46
SUBCLASS PROFILE
Pattern A (large)
Pattern AB (intermediate)
Pattern B (small)
48
LDL Size 41
nm 41b
19.6 41a
20.6-22.0 46a
20.4-20.5 46b
19.0-20.3 46c
Lower-Risk
Higher-Risk
LDL Particles 42
nmol/L 42b
2205 42a
Percentage of population with a lower level 42c
0% 25% 50% 75% 100% 46' (94%)
Lower CHD Risk Higher
Large HDL Cholesterol 43
mg/dL 43b
21 43a
Percentage of population with a higher level 43c
0% 25% 50% 75% 100% 46' (71%)
Lower CHD Risk Higher
Large VLDL Triglyceride 44
mg/dL 44b
30 44a
Percentage of population with a lower level 44c
0% 25% 50% 75% 100% 46' (78%)
Lower CHD Risk Higher
Population percentages are based on data obtained from analysis of 3,437 subjects in the Framingham Offspring Study.

FIG. 4.

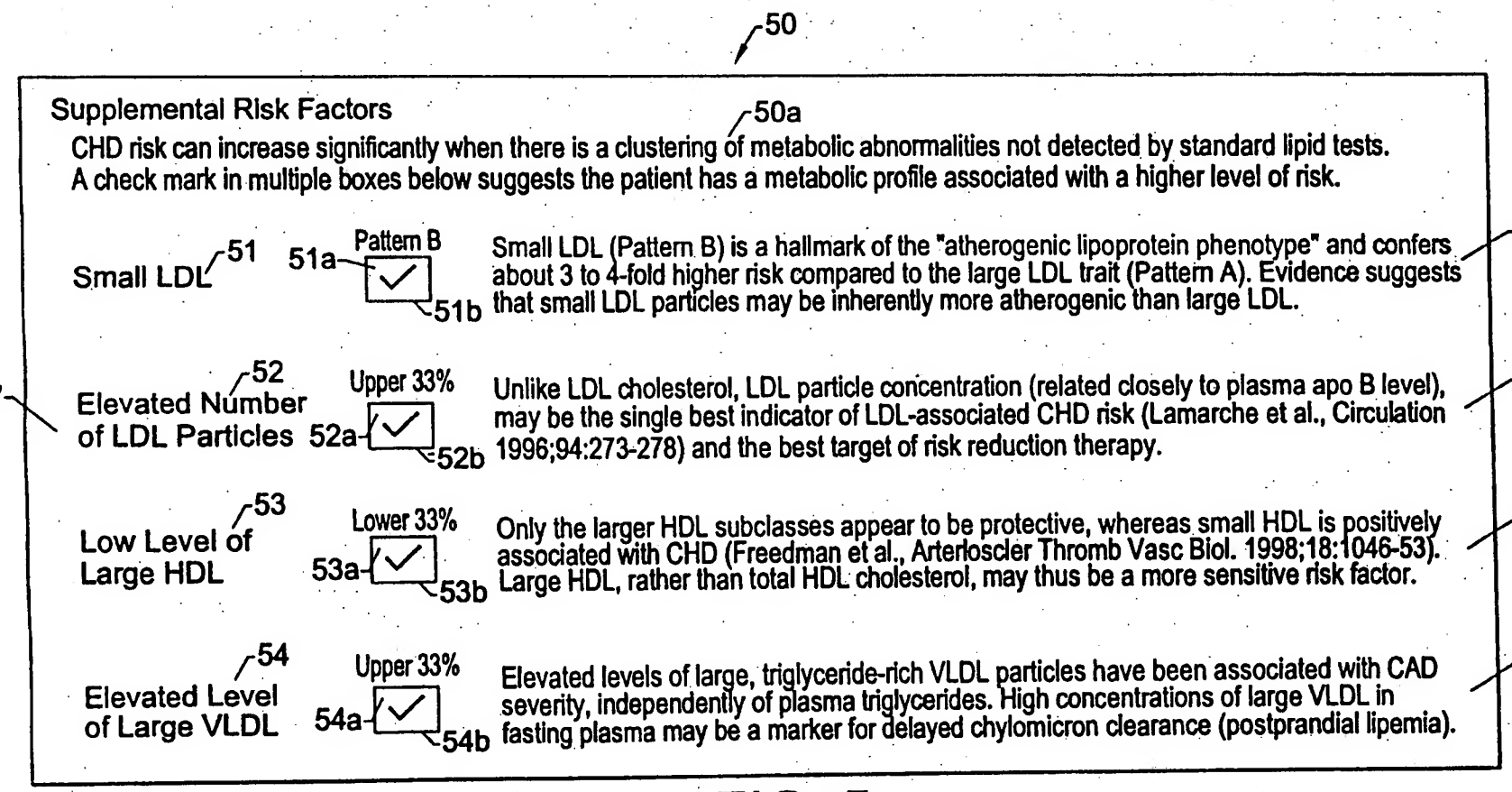


FIG. 5.

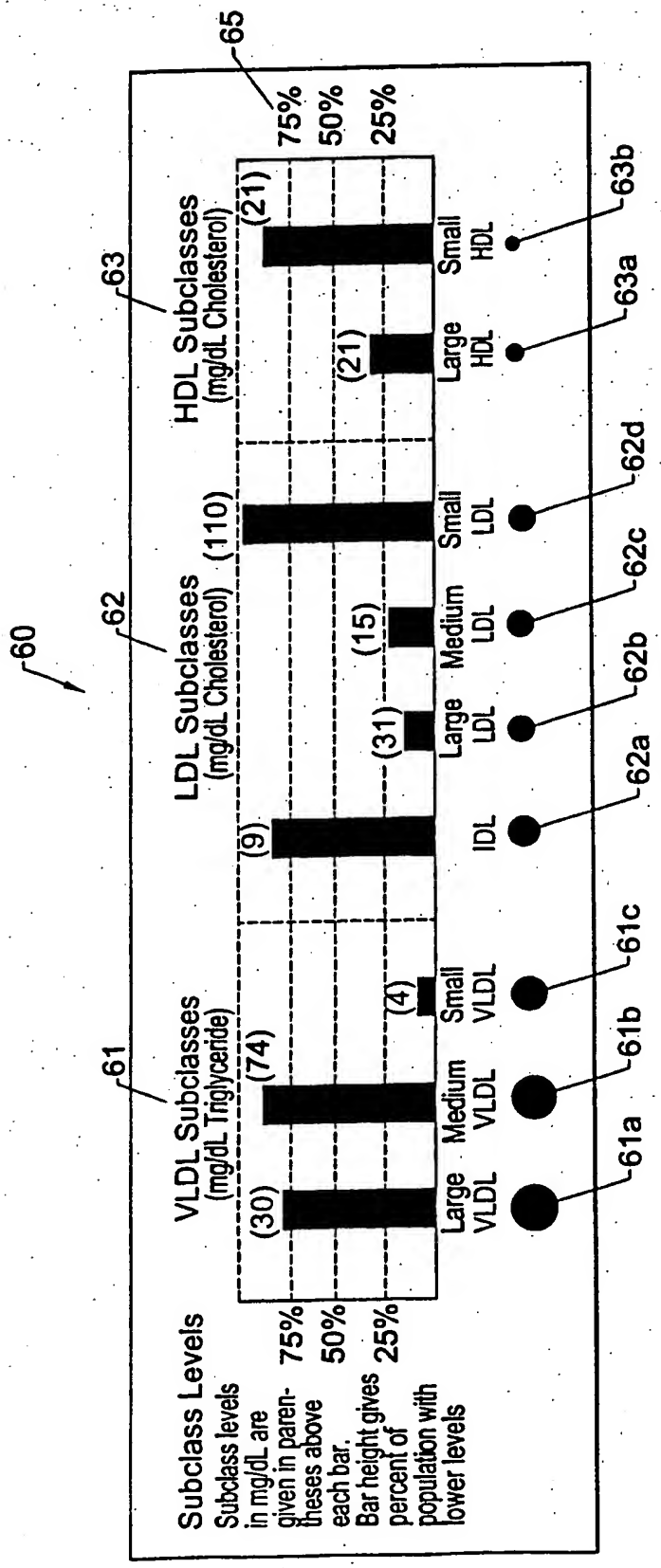

60
61
62
63
65
VLDL Subclasses (mg/dL Triglyceride)
LDL Subclasses (mg/dL Cholesterol)
HDL Subclasses (mg/dL Cholesterol)
75%
50%
25%
(30)
(74)
(4)
(9)
(31)
(15)
(110)
(21)
(21)
Large VLDL
Medium VLDL
Small VLDL
IDL
Large LDL
Medium LDL
Small LDL
Large HDL
Small HDL
61a
61b
61c
62a
62b
62c
62d
63a
63b
Subclass Levels
Subclass levels in mg/dL are given in parentheses above each bar. Bar height gives percent of population with lower levels
75%
50%
25%

FIG. 6.

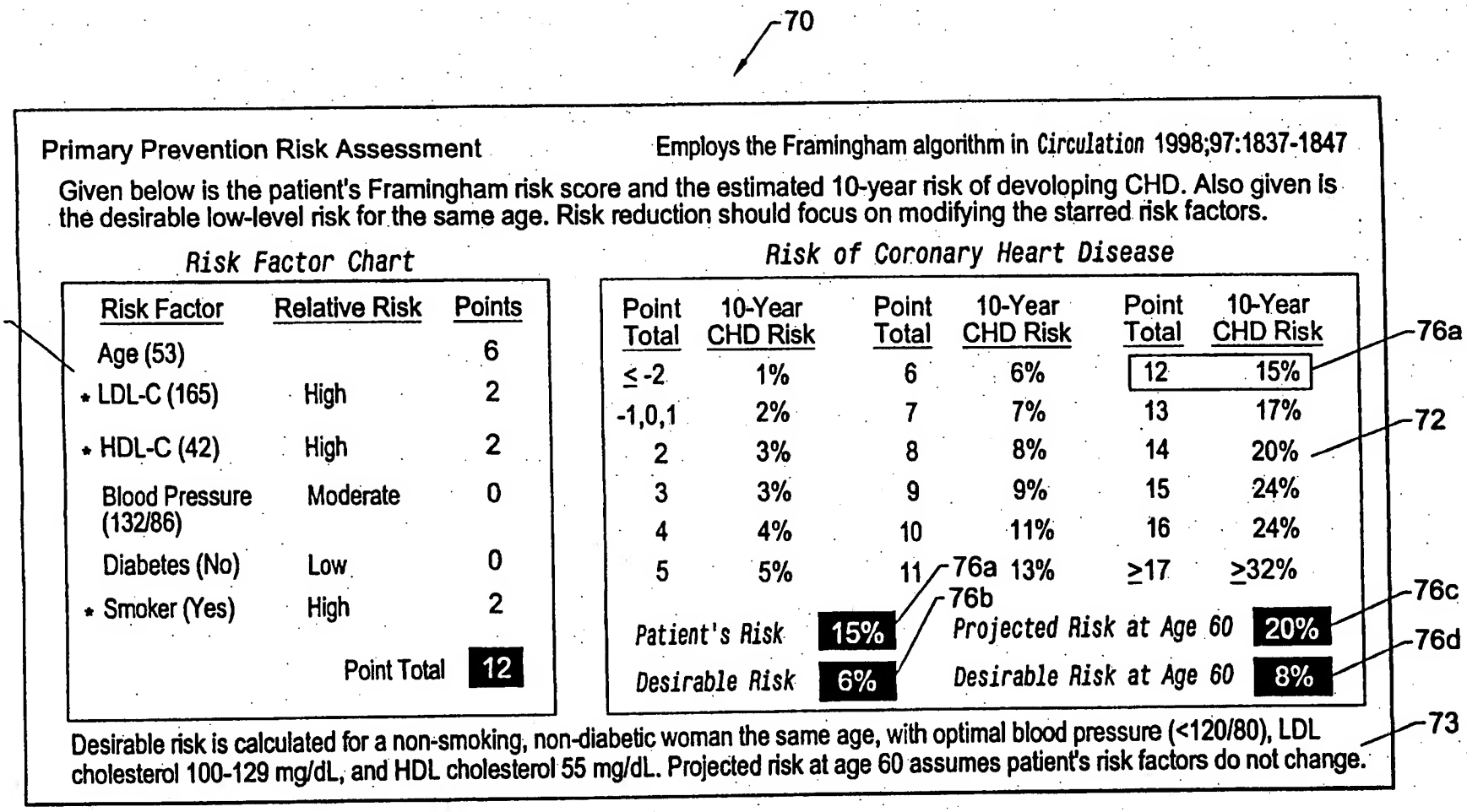


FIG. 7.

Positive Risk Factor Chart	Relative Risk	Points
HDL-C ≥ 60	Negative	-1
LDL Size Pattern A	Negative	-2
Elevated Large HDL	Negative	-1
Exercise	Negative	-1

FIG. 7A.

80

Secondary Prevention Guidelines

Patients with established CHD, other atherosclerotic vascular disease, or diabetes are considered to be at particularly high risk by the NCEP. The primary goal of lipid management should be the reduction of LDL cholesterol to under 100 mg/dL. The corresponding NMR LDL particle concentration target is 1100 nmol/L. For patients with small LDL (pattern B) and a clustering of the supplemental risk factors shown above, it is especially important to reach these LDL goals. Smoking cessation, increased exercise, healthy diet, and blood pressure control are also important treatment goals.

80a

FIG. 8.

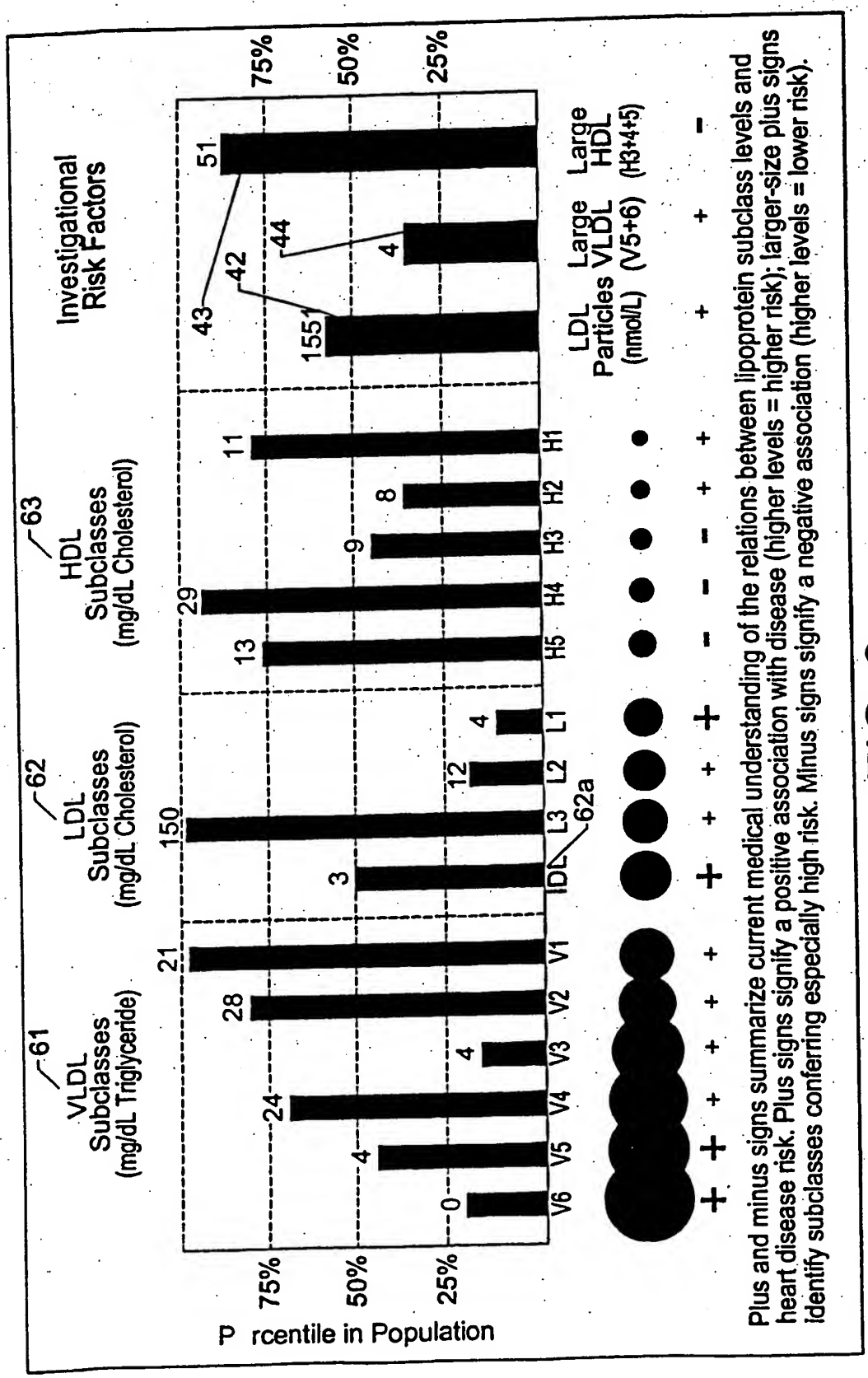
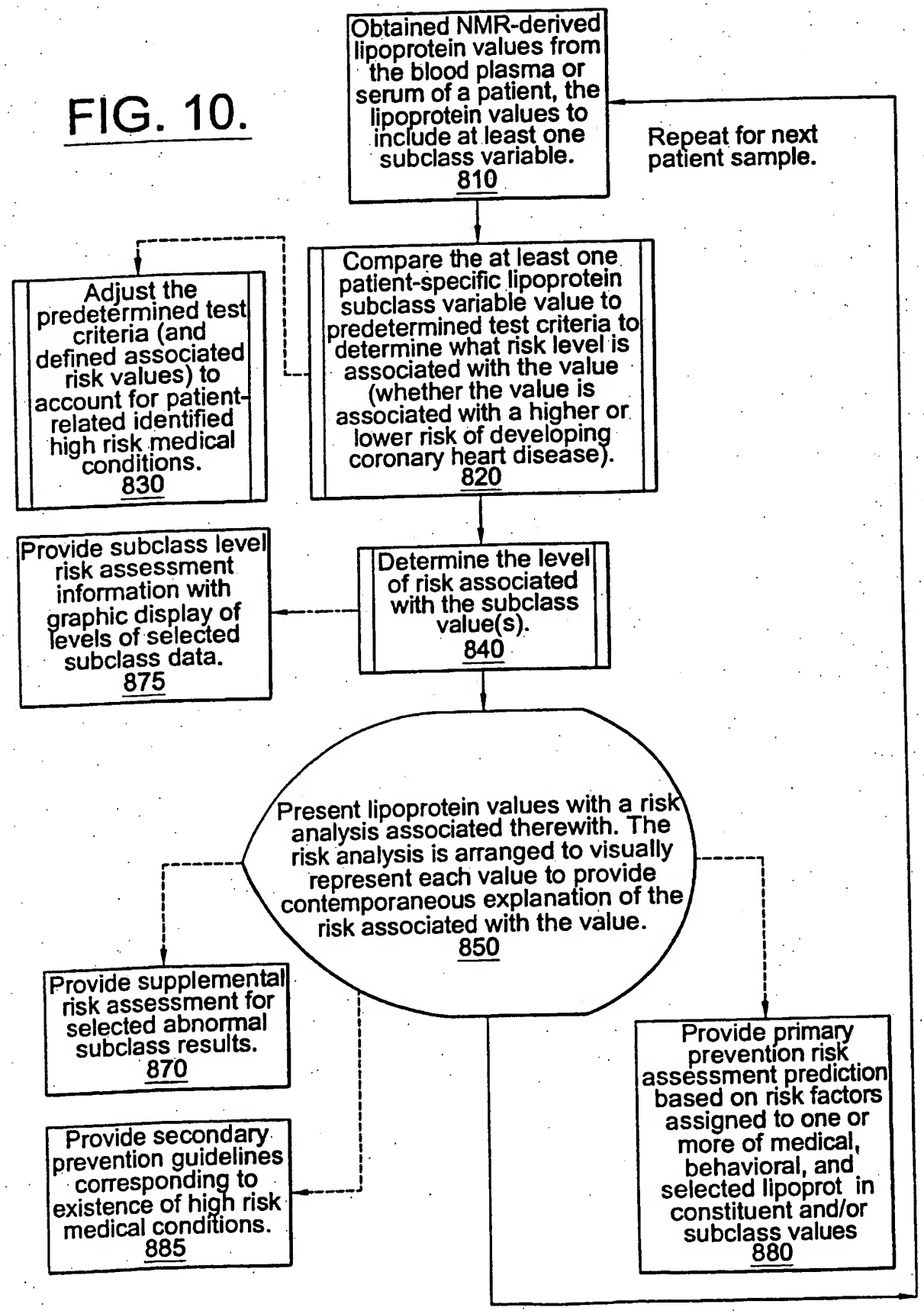

Investigational Risk Factors
61
VLDL Subclasses (mg/dL Triglyceride)
62
LDL Subclasses (mg/dL Cholesterol)
63
HDL Subclasses (mg/dL Cholesterol)
LDL Particles (nmol/L)
Large VLDL (V5+6)
Large HDL (H3+4+5)
V6 V5 V4 V3 V2 V1 IDL L1 L2 L3 H5 H4 H3 H2 H1
62a
0 4 24 28 21 3 150 4 12 13 29 9 8 11
155 43 42 44 4 51
25% 50% 75%
Percentile in Population
Plus and minus signs summarize current medical understanding of the relations between lipoprotein subclass levels and heart disease risk. Plus signs signify a positive association with disease (higher levels = higher risk); larger-size plus signs identify subclasses conferring especially high risk. Minus signs signify a negative association (higher levels = lower risk).

FIG. 9.

FIG. 10.


Obtained NMR-derived lipoprotein values from the blood plasma or serum of a patient, the lipoprotein values to include at least one subclass variable.
810
Repeat for next patient sample.
Compare the at least one patient-specific lipoprotein subclass variable value to predetermined test criteria to determine what risk level is associated with the value (whether the value is associated with a higher or lower risk of developing coronary heart disease).
820
Adjust the predetermined test criteria (and defined associated risk values) to account for patient-related identified high risk medical conditions.
830
Determine the level of risk associated with the subclass value(s).
840
Provide subclass level risk assessment information with graphic display of levels of selected subclass data.
875
Present lipoprotein values with a risk analysis associated therewith. The risk analysis is arranged to visually represent each value to provide contemporaneous explanation of the risk associated with the value.
850
Provide supplemental risk assessment for selected abnormal subclass results.
870
Provide secondary prevention guidelines corresponding to existence of high risk medical conditions.
885
Provide primary prevention risk assessment prediction based on risk factors assigned to one or more of medical, behavioral, and selected lipoprot in constituent and/or subclass values
880

Page 1 of 2

NMR LipoProfile™ Summary Report

10'''

Patient Name	Sex	Age
Patient #5		

Patient ID	Birth Date	Specimen ID
		LP001141

Data Collected	Data Received	Date Reported
	04-02-99	04-05-99

Physician Name & Address

Phone: ( )
FAX: ( )

Comments

LIPID PROFILE

	mg/dL	Current NCEP Risk Categories: Desirable (36a)	Borderline-High (36b)	High (36c)
Total Cholesterol (31')	219 (31a') (31b)	less than 200	200-239	240 or greater

	mg/dL	Optimal* (36d)	Desirable (36)	Borderline-High (36)	High Risk (36)
LDL Concentration (cholesterol equivalents) (32') (30')	142 (32a') (32b)	less than 100	100-129	130-159	greater than 160

	mg/dL	Negative Risk Factor (36)	Intermediate (36)	Positive Risk Factor
HDL Concentration (cholesterol equivalents) (33')	32 (33a') (33b)	60 or greater	59-35	less than 35

	mg/dL	Desirable (36)	Borderline-High (36)	High (36)
Triglycerides (34)	330 (34a') (34b)	less than 200	200-400	400-1,000

Lipid profile values are determined by measuring plasma lipoprotein levels directly by NMR, and converting concentrations to cholesterol or triglyceride units assuming that each lipoprotein has a normal lipid composition. For most patients, NMR and standard lipid panel values agree closely. Patients with certain metabolic abnormalities or elevated triglycerides may have cholesterol-depleted LDL. In these cases, LDL concentrations determined by NMR will be higher than those inferred by standard LDL cholesterol tests.

SUBCLASS PROFILE

		Optimal*	Desirable (146)	Borderline-High	High Risk
LDL Particles (42')	nmol/L 1925 (42a') (42b')	less than 1100	1100-1399	1400-1799	greater than 1800

		Pattern A (large LDL)	Intermediate Size	Pattern B (small LDL)
LDL Size (41') (40')	nm 19.5 (41a') (41b')	20.6-22.0 Lower-Risk	20.5-20.4	20.3-19.0 Higher-Risk

		Negative Risk Factor	Intermediate	Positive Risk Factor
Large HDL (cholesterol) (43')	mg/dL 11 (43a') (43b')	greater than 42	42-18	less than 18

		Lower-Risk	Intermediate	Higher-Risk
Large VLDL (triglyceride) (44')	mg/dL 110 (44a') (44b')	less than 7	7-33	greater than 33

146

LDL Particle concentration categories correspond to NCEP categories for LDL cholesterol (on a percentile equivalence basis), and provide an alternative target for therapy. Large HDL is the protective component of HDL-levels below the 20th percentile indicate higher risk (positive risk factor) and above the 80th percentile lower risk (negative risk factor). Elevations of Large VLDL are related to delayed chylomicron clearance and higher CHD risk-values above the 80th percentile define the "higher-risk" category.

*Goal for secondary prevention (patients with established CHD or diabetes)

FIG. 11.

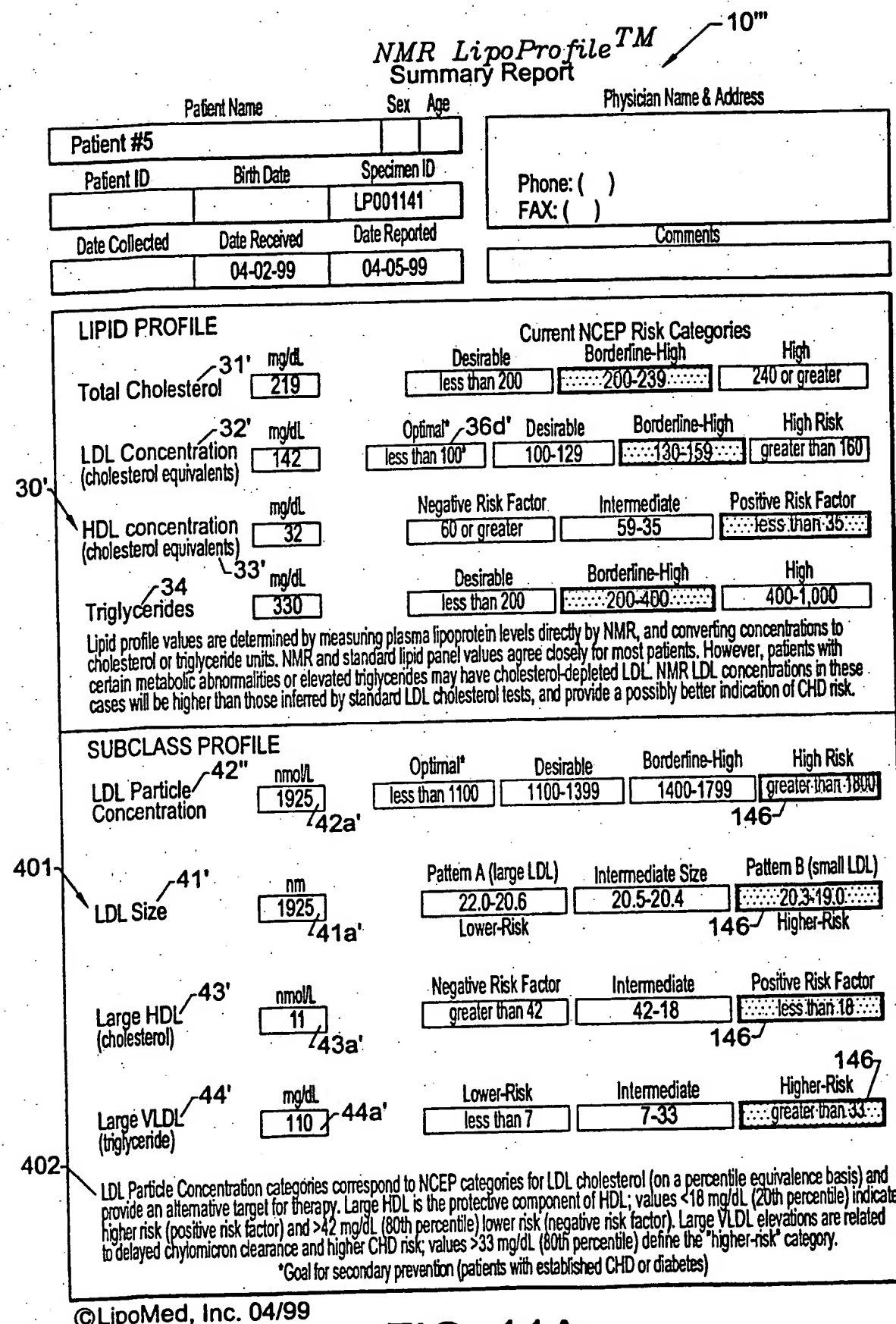

NMR LipoProfile™
10'''
Summary Report
Patient Name
Sex
Age
Patient #5
Physician Name & Address
Patient ID
Birth Date
Specimen ID
LP001141
Phone: ( )
FAX: ( )
Date Collected
Date Received
Date Reported
04-02-99
04-05-99
Comments
LIPID PROFILE
Current NCEP Risk Categories
Total Cholesterol
31'
mg/dL
219
Desirable
Borderline-High
High
less than 200
200-239
240 or greater
LDL Concentration
(cholesterol equivalents)
32'
mg/dL
142
Optimal*
36d'
Desirable
Borderline-High
High Risk
less than 100*
100-129
130-159
greater than 160
30'
HDL concentration
(cholesterol equivalents)
33'
mg/dL
32
Negative Risk Factor
Intermediate
Positive Risk Factor
60 or greater
59-35
less than 35
Triglycerides
34
mg/dL
330
Desirable
Borderline-High
High
less than 200
200-400
400-1,000
Lipid profile values are determined by measuring plasma lipoprotein levels directly by NMR, and converting concentrations to cholesterol or triglyceride units. NMR and standard lipid panel values agree closely for most patients. However, patients with certain metabolic abnormalities or elevated triglycerides may have cholesterol-depleted LDL. NMR LDL concentrations in these cases will be higher than those inferred by standard LDL cholesterol tests, and provide a possibly better indication of CHD risk.
SUBCLASS PROFILE
LDL Particle Concentration
42"
nmol/L
1925
42a'
Optimal*
Desirable
Borderline-High
High Risk
less than 1100
1100-1399
1400-1799
greater than 1800
146
401
LDL Size
41'
nm
1925
41a'
Pattern A (large LDL)
Intermediate Size
Pattern B (small LDL)
22.0-20.6
20.5-20.4
20.3-19.0
Lower-Risk
146
Higher-Risk
Large HDL
(cholesterol)
43'
nmol/L
11
43a'
Negative Risk Factor
Intermediate
Positive Risk Factor
greater than 42
42-18
less than 18
146
146
Large VLDL
(triglyceride)
44'
mg/dL
110
44a'
Lower-Risk
Intermediate
Higher-Risk
less than 7
7-33
greater than 33
402
LDL Particle Concentration categories correspond to NCEP categories for LDL cholesterol (on a percentile equivalence basis) and provide an alternative target for therapy. Large HDL is the protective component of HDL; values <18 mg/dL (20th percentile) indicate higher risk (positive risk factor) and >42 mg/dL (80th percentile) lower risk (negative risk factor). Large VLDL elevations are related to delayed chylomicron clearance and higher CHD risk; values >33 mg/dL (80th percentile) define the "higher-risk" category.
*Goal for secondary prevention (patients with established CHD or diabetes)
©LipoMed, Inc. 04/99

FIG. 11A.

NMR LipoProfile™ 100
Technical Report

Patient Name: Patient #5 | Specimen ID: LP001141 | Date Reported: 04-05-99

150

CHD RISK ASSESSMENT MODULE

151 Elevated Number of LDL Particles — Upper 50% ☑ (151a)
Unlike LDL cholesterol, LDL particle concentration (related closely to plasma apo B level), may be the single best indicator of LDL-associated CHD risk (Lamarche et al., Circulation 1996;94:273-278) and the best target of risk reduction therapy.

152 Atherogenic Dyslipidemia ☑
Patients with a clustering of the lipoprotein subclass abnormalities listed below are at higher risk of CHD when LDL particle numbers are elevated. Check marks in 2 or more of the boxes below indicate the presence of this higher-risk metabolic condition.

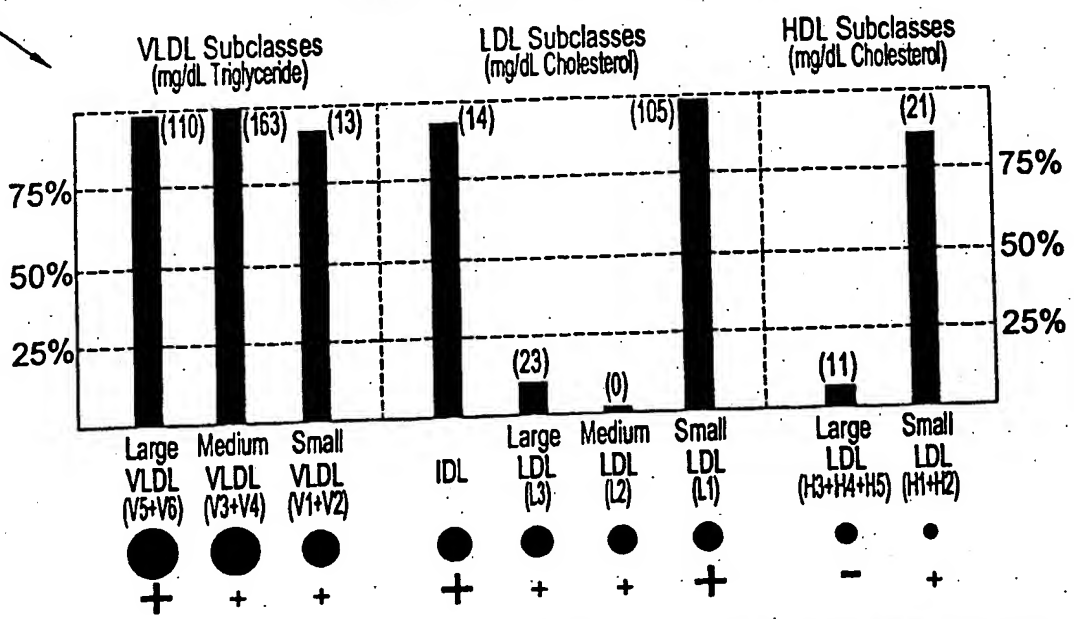
* Small LDL (153) Pattern B ☑ (153a)
Small LDL (Pattern B) is a hallmark of "atherogenic dyslipidemia" and confers about three-fold higher risk compared to the large LDL trait (Pattern A). Evidence suggests that small LDL particles may be inherently more atherogenic than large LDL.

154 * Low Level of Large HDL — Lower 33% ☑ (154a)
Only the larger HDL subclasses appear to be protective, whereas small HDL is positively associated with CHD (Freedman et al., Arterioscler Thromb Vasc Biol. 1998;18:1046-53). Large HDL, rather than total HDL cholesterol, may thus be a more sensitive risk factor.

155 * Elevated Level of Large VLDL — Upper 33% ☑ (155a)
Elevated levels of large, triglyceride-rich VLDL particles have been associated with CAD severity, independently of plasma triglycerides. High concentrations of large VLDL in fasting plasma are a marker for delayed chylomicron clearance (postprandial lipemia).

SUBCLASS LEVELS
Lipoprotein subclass levels (mg/dL) are given in parentheses above each bar. The height of the bar gives the percent of the population* with equal or lower levels.

60'



The plus and minus signs shown above summarize current medical understanding of the relations between lipoprotein subclass levels and heart disease risk. Plus signs signify a positive association with disease (higher levels = higher risk). Larger plus signs signify especially high-risk subclasses. The minus sign signifies a negative association with disease (higher levels = lower risk).

*Population percentile values are from NMR data obtained from analysis of 3,437 subjects in the Framingham Offspring Study.

FIG. 12.

NMR LipoProfile™ 100
Technical Report

Patient Name	Specimen ID	Date Reported
Patient #5	LP001141	04-05-99

150'

CHD RISK ASSESSMENT MODULE

151 Elevated Number Particle Conc. 151a' Upper 50% ☑ — LDL particle concentration (related to plasma apo B level) may be the single best indicator of LDL-associated CHD risk (Lamarche et al., Circulation 1996;94:273-278) and the best target of risk reduction therapy. Levels >1400 nmol/L (30th percentile) are "elevated".

152 Atherogenic Dyslipidemia ☑ — Patients with a clustering of the lipoprotein subclass abnormalities listed below are at higher risk of CHD when LDL particle concentration is elevated. Check marks in 2 or more of the boxes below indicate the presence of this higher-risk metabolic condition.

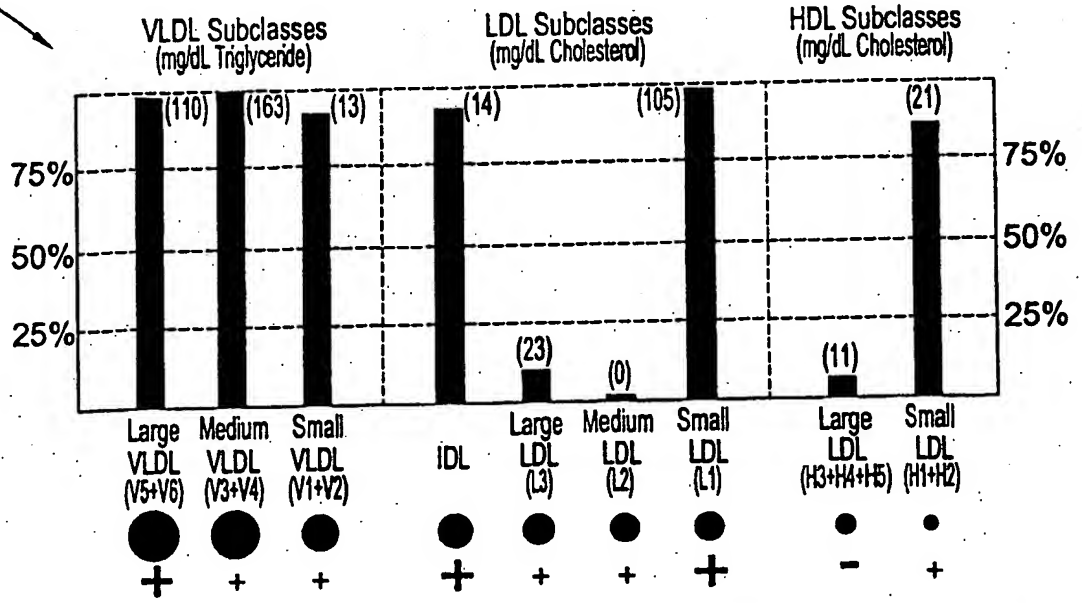
* Small LDL 153 Pattern B 153a' ☑ — Small LDL (Pattern B) is a hallmark of "atherogenic dyslipidemia" and confers about three-fold higher risk compared to the large LDL trait (Pattern A). Evidence suggests that small LDL particles may be inherently more atherogenic than large LDL.

154 * Low Level of Large HDL <23 mg/dL 154a' ☑ — Only the larger HDL subclasses appear to be protective, whereas small HDL is positively associated with CHD (Freedman et al., Arterioscler Thromb Vasc Biol. 1998;18:1045-53). Large HDL levels <23 mg/dL (35th percentile) are defined as "low".

155 * Elevated Level of Large VLDL >17mg/dL 155a ☑ — Elevated levels of large VLDL subclasses in fasting plasma are associated with CAD severity independently of plasma triglycerides, and are a marker for delayed chylomicron clearance. Large VLDL levels>17 mg/dL (65th percentile) are defined as "elevated".

SUBCLASS LEVELS — Lipoprotein subclass levels (mg/dL) are given in parentheses above each bar. The height of the bar gives the percent of the population* with equal or lower levels.

60'



The plus and minus signs shown above summarize current medical understanding of the relations between lipoprotein subclass levels and heart disease risk. Plus signs signify a positive association with disease (higher levels = higher risk). Larger plus signs signify especially high-risk subclasses. The minus sign signifies a negative association with disease (higher levels = lower risk).

*Population percentile values are from NMR data obtained from analysis of 3,437 subjects in the Framingham Offspring Study.

FIG. 12A.

NMR LipoProfile DM 110
Heart Disease Report

Patient Name		Sex	Age
Patient #5			

Patient ID	Birth Date	Specimen ID
		LP001141

Date Collected	Date Received	Date Received
	04-02-99	04-05-99

Physician Name & Address

Phone: ( )
FAX: ( )

Comments

SUBCLASS PROFILE

401

		Optimal*	Desirable	Borderline-High	High Risk
LDL Particle Concentration	nmol/L 1925	less than 1100	1100-1399	1400-1799	greater than 1800

		Pattern A (large LDL)	Intermediate Size	Pattern B (small LDL)
LDL Size	nm 19.5	22.0-20.8 Lower-Risk	20.5-20.4	20.3-19.0 Higher-Risk

		Negative Risk Factor	Intermediate	Positive Risk Factor
Large HDL (cholesterol)	mg/dL 11	greater than 42	42-18	less than 18

		Lower-Risk	Intermediate	Higher-Risk
Large VLDL (triglyceride)	mg/dL 110	less than 7	7-33	greater than 33

LDL Particle Concentration categories correspond to NCEP categories for LDL cholesterol (on a percentile equivalence basis) and provide an alternative target for therapy. Large HDL is the protective component of HDL; values <18 mg/dL (20th percentile) indicate higher risk (positive risk factor) and >42 mg/dL (80th percentile) lower risk (negative risk factor). Large VLDL elevations are related to delayed chylomicron clearance and higher CHD risk; values >33 mg/dL (80th percentile) define the "higher-risk" category.

*Goal for secondary prevention (patients with established CHD or diabetes)

150'

CHD RISK ASSESSMENT MODULE

151 Elevated LDL Particle Conc.	>1400 nmol/L ☑	LDL particle concentration (related to plasma apo B level) may be the single best indicator of LDL-associated CHD risk (Lamarche et al., Circulation 1996;94:273-278) and the best target of risk reduction therapy. Levels>1400 nmol/L (50th percentile) are "elevated".
152 Atherogenic Dyslipidemia	☑	Patients with a clustering of the lipoprotein subclass abnormalities listed below are at higher risk of CHD when LDL particle concentration is elevated. Check marks in 2 or more of the boxes below indicate the presence of this higher-risk metabolic condition.
* Small LDL 153	Pattern B ☑	Small LDL (Pattern B) is a hallmark of "atherogenic dyslipidemia" and confers about three-fold higher risk compared to the large LDL trait (Pattern A). Evidence sggests that small LDL particles may be inherently more atherogenic than large LDL.
* Low Level of Large HDL 154	<23 mg/dL ☑	Only the larger HDL subclasses appear to be protective, whereas small HDL is positively associated with CHD (Freedman et al., Arterioscler Thromb Vasc Biol. 1998;18:1046-53). Large HDL levels <23 mg/dL (35th percentile) are defined as "low".
* Elevated Level of Large VLDL 155	>17 mg/dL ☑	Elevated levels of large VLDL subclasses in fasting plasma are associated with CAD severity independently of plasma triglycerides, and are a marker for delayed chylomicron clearance. Large VLDL levels >17 mg/dL (65th percentile) are defined as "elevated".

FIG. 13.

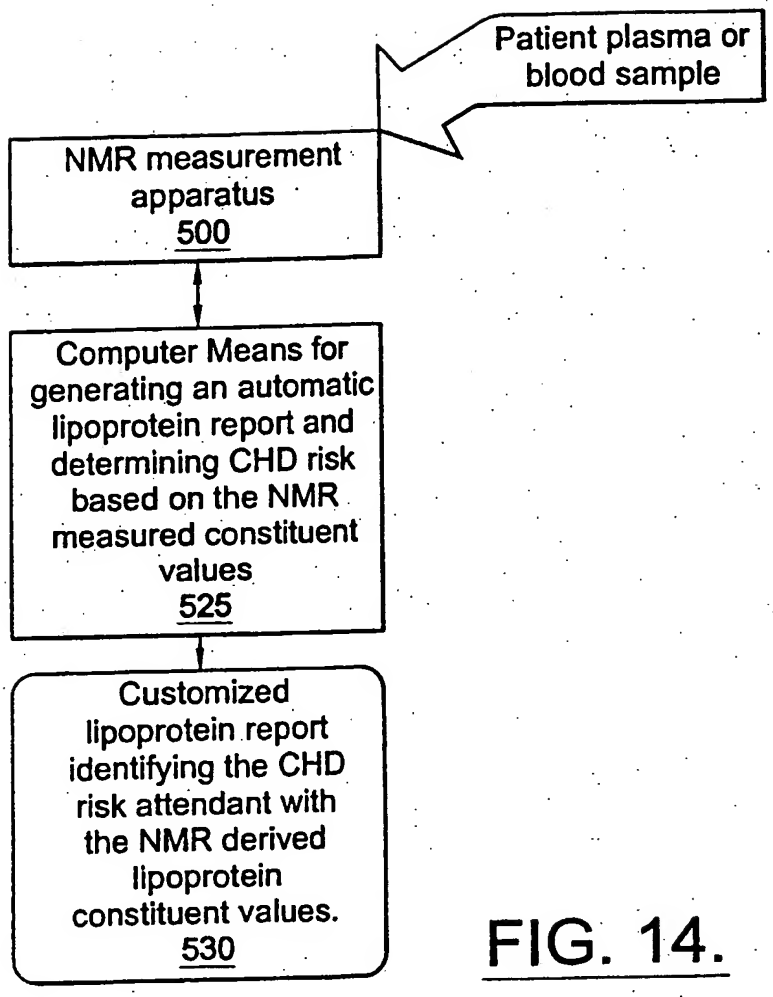

Patient plasma or blood sample
NMR measurement apparatus 500
Computer Means for generating an automatic lipoprotein report and determining CHD risk based on the NMR measured constituent values 525
Customized lipoprotein report identifying the CHD risk attendant with the NMR derived lipoprotein constituent values. 530

FIG. 14.

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/US 99/29730

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G06F19/00 G01R33/465 G01N33/483 G01N33/92 G01N33/487

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G06F G01R G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	D.S. FREEDMAN ET AL: "Relation of Lipoprotein Subclasses as Measured by Proton Nuclear Magnetic Resonance Spectroscopy to Coronary Artery Disease" ARTERIOSCLEROSIS THROMBOSIS AND VASCULAR BIOLOGY, vol. 18, no. 7, 1998, pages 1046-1053, XP002139895 USA cited in the application page 1051, left-hand column, line 21 -page 1052, left-hand column, line 37 page 1047, right-hand column, line 54 -page 1051, left-hand column, line 16 page 1047, left-hand column, line 39 -right-hand column, line 40 page 1046, right-hand column, line 8 - line 18 --- -/--	1-12, 16-29

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 June 2000	06/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Barba, M

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"Magnetic Resonance Test may give better assessment of Heart Disease Risk" DOCTOR'S GUIDE, 'Online! 1 July 1998 (1998-07-01), pages 1-3, XP002139896 USA Retrieved from the Internet: <URL:http://www.pslgroup.com/dg/8DE5A.htm> 'retrieved on 2000-06-08! page 1, line 1 -page 2, line 21 ---	1-12, 16-29
X	"Company Profile: Lipomed technology anticipated to be a leading Predictor of Heart Disease" BT CATALYST, 'Online! February 1998 (1998-02), pages 1-3, XP002139897 USA Retrieved from the Internet: <URL:http://www.ncbiotech.org/feb98-4.htm> 'retrieved on 2000-06-08! page 1, line 15 -page 2, line 9 ---	1-12, 16-29
X	"New test more accurately measures Risk of Heart Disease, Study finds" NC STATE UNIVERSITY DOCUMENT VIEW, 'Online! 13 July 1998 (1998-07-13), pages 1-6, XP002139898 USA Retrieved from the Internet: <URL:http://search.ncsu.edu> 'retrieved on 2000-06-08! page 1, line 8 -page 3, line 20 page 3, line 36 -page 4, line 4 ---	1-12, 16-29
A	WO 93 03450 A (UNIV NORTH CAROLINA) 18 February 1993 (1993-02-18) page 3, line 28 -page 5, line 12 page 6, line 11 -page 10, line 20 page 14, line 8 - line 17 page 16, line 3 - line 26 ---	1-12, 16-29
A	WO 91 10128 A (BETH ISRAEL HOSPITAL) 11 July 1991 (1991-07-11) page 3, line 17 -page 4, line 6 page 4, line 2 -page 6, line 3 page 8, line 17 -page 11, line 10 --- -/—	1-12, 16-29

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	ALA-KORPELA M ET AL: "QUANTIFICATION OF BIOMEDICAL NMR DATA USING ARTIFICIAL NEURAL NETWORK ANALYSIS: LIPOPROTEIN LIPID PROFILES FROM 1H NMR DATA OF HUMAN PLASMA" NMR IN BIOMEDICINE,GB,WILEY, LONDON, vol. 8, no. 6, 1 September 1995 (1995-09-01), pages 235-244, XP000670783 ISSN: 0952-3480 page 235, right-hand column, line 15 -page 236, left-hand column, line 27 page 236, right-hand column, line 21 -page 237, left-hand column, line 42 page 238, left-hand column, line 10 -right-hand column, line 56 page 240, right-hand column, line 5 -page 243, left-hand column, line 27 ---	1-12, 16-29
L	"Size matters - When it comes to Cholesterol Particles and Heart Disease Risk" PRESS RELEASE , 'Online! 14 April 1999 (1999-04-14), pages 1-3, XP002139899 USA Retrieved from the Internet: <URL:http://www.lipoprofile.com/press_release2.html> 'retrieved on 2000-06-08! Cited because it refers to a possible disclosure of the present invention to the public before the claimed priority date page 2, line 34 - line 36 -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/US 99/29730

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9303450 A	18-02-1993	AU 2384292 A	02-03-1993
		US 5343389 A	30-08-1994
WO 9110128 A	11-07-1991	AU 7142991 A	24-07-1991
		BR 9007936 A	27-10-1992
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		JP 6505089 T	09-06-1994